American Heart Journal

VOL. 44 OCTOBER, 1952 No. 4

Original Communications

THE OCCURRENCE IN PAROXYSMAL VENTRICULAR TACHYCARDIA OF VENTRICULAR COMPLEXES TRANSITIONAL IN SHAPE TO SINOAURICULAR BEATS

A DIAGNOSTIC AID

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THE ESSENTIAL diagnostic criterion of paroxysmal ventricular tachycardia, besides bizarre shape of the ventricular complexes, is the finding of an independent atrial rhythm which, as a rule, is slower than the ventricular rhythm.[1-4] In the absence of this sign, it is generally agreed that the diagnosis of paroxysmal ventricular tachycardia is uncertain, for the abnormality of the ventricular beats may be due to pre-existing bundle branch block or to aberrant intraventricular conduction secondary to tachycardia of supraventricular origin. The differential diagnosis of the two forms of tachycardia is important because the ventricular type has a more serious connotation and requires a different treatment than does tachycardia of supraventricular origin.

In a good number of cases of paroxysmal ventricular tachycardia, evidence of an independent atrial rhythm is lacking, either because the P waves are inconspicuous, or, if well developed, are obscured by large ventricular deflections; or because irregularity of the sinus rhythm renders it difficult to elicit signs of an independent, rhythmical action of the atria. The finding of ventricular complexes resembling in shape sinoauricular beats, without disturbance of the regular ventricular rhythm, may be a diagnostic aid. Such variations in the configuration of the ventricular beats are usually due to sinus excitations which are able to travel down the junctional tissues and to activate part or all of the ventricle. In the first case, they produce ventricular fusion beats; in the latter case, sinoauricular beats. The occurrence of ventricular complexes of varying shape in the presence of paroxysmal ventricular tachycardia is illustrated by the following electrocardiograms.

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Received for publication May 3, 1952.

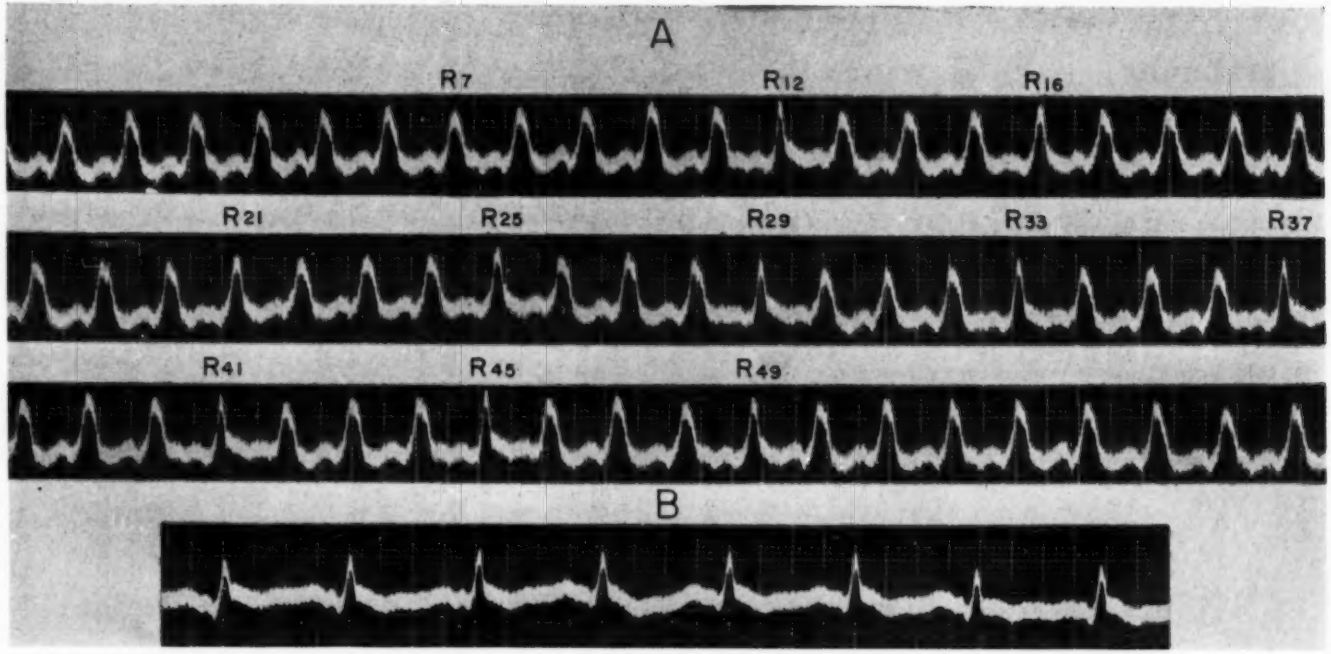

Fig. 1.—*A*, Lead I. Three strips form a continuous tracing. Regular ventricular tachycardia; rate, 143. Most of the R deflections are broad-topped and slurred. Some beats, however, show peaked, narrow R waves (R_{12}, R_{29}, R_{33}, R_{37}, R_{41}, and R_{45}) which resemble the sinoauricular beats of Fig. 1,*B*. Other QRS complexes (R_{16}, R_{21}, R_{25}, and R_{49}) are intermediate in shape between the two types of ventricular beats. The ventricular systoles, which differ in shape from the majority of the beats, are preceded by P waves which are mostly superimposed on the concavity of the S-T segments. These atrial excitations are obviously conducted to the ventricles and produce, depending on their time of incidence, either ventricular fusion beats or ventricular complexes closely resembling sinoauricular beats. The regularity of the ventricular rhythm is not disturbed.

B, Lead I. Shows return of sinus rhythm after cessation of the tachycardia.

Figs. 1 to 3 are electrocardiograms of a 69-year-old woman who, following coronary thrombosis, suffered numerous attacks of paroxysmal tachycardia, which apparently originated in various ventricular foci. Fig. 1,*A*, shows 3 strips of Lead I which form a continuous tracing. A regular tachycardia with a rate of 143 per minute is present. The ventricular cycle measures 0.40 to 0.44 second. The duration of QRS is 0.18 second. The bizarre shape of the ventricular complexes suggests a tachycardia of ventricular origin. An independent atrial rhythm is suggested by irregularities of the base line but is not distinctly recognizable. However, variations in the shape of the ventricular beats suggest that some sinus excitations might exert an effect on ventricular systoles. While most of the ventricular complexes present a broad-topped, slurred, main deflection, some have narrow, sharply peaked R waves (R_{12}, R_{29}, R_{33}, R_{37}, R_{41}, and R_{45}); other QRS complexes (R_{16}, R_{21}, R_{25}, and R_{49}) seem to be intermediate in shape between these two types of ventricular beats. It can be noted that the ventricular complexes which differ in shape from the average beats are preceded by upright waves, which are superimposed on the concavity of the S-T segments and obviously represent atrial excitations. Some of these reach the lower chamber early enough to activate almost all of the ventricle. The resulting ventricular beats (R_{12}, R_{29}, R_{33}, R_{37}, R_{41}, and R_{45}) are practically identical in shape with the sinoauricular beats of Fig. 1,*B*.

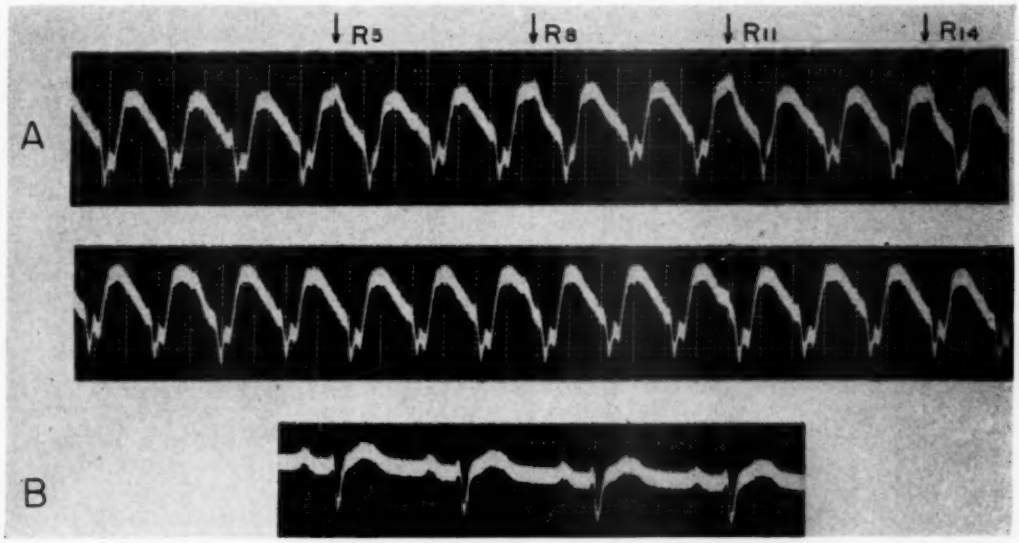

Fig. 2.—*A*, Lead II. Two strips form a continuous tracing. Regular ventricular tachycardia; rate, 148. The ventricular complexes are of bizarre shape; some of them (R_5, R_8, R_{11}, and R_{14}) differ slightly in configuration and show narrower QRS complexes. They are preceded by P waves (arrow) which are superimposed on the summit of T. These represent atrial excitations which are conducted to the ventricles and cause ventricular fusion beats. The regularity of the ventricular rhythm is not disturbed. The lower strip of the tracing shows neither distinct signs of an independent atrial rhythm nor ventricular fusion beats.

B, Lead II. Shows the restored sinus rhythm after cessation of the tachycardia. It can be noted that R_5, R_8, R_{11}, and R_{14} of the top strip are intermediate in shape between the sinoauricular beats and the bizarre ventricular complexes of the ventricular tachycardia.

Other sinus excitations reach the ventricles somewhat later, and interfere with the simultaneously released ventricular excitations. They give rise to the appearance of ventricular fusion beats, (R_{16}, R_{21}, R_{25}, and R_{49}). Neither of these beats disturb the regularity of the ventricular rhythm. Obviously some atrial waves (as, for instance, the P wave following R_7) are too early to be conducted to the ventricles, and have therefore no effect on the following systole.

Fig. 1,*B* (Lead I) was obtained after termination of the tachycardia and shows sinoauricular rhythm.

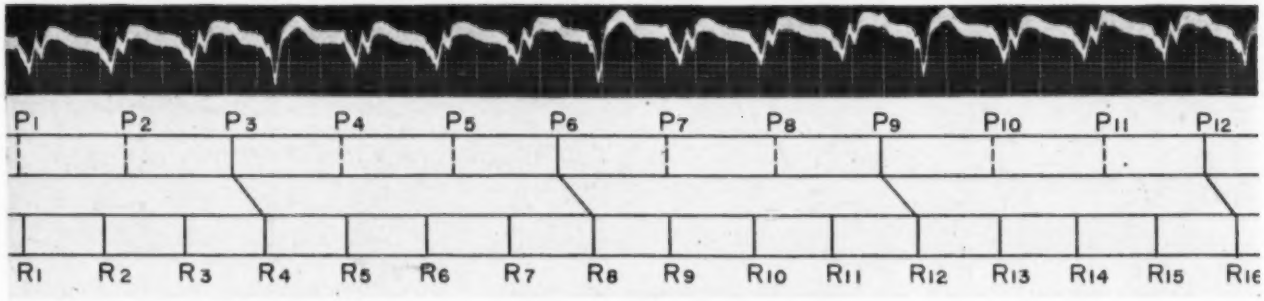

Fig. 3.—Lead aVF. Regular ventricular tachycardia; rate, 113 per minute. The ventricular beats are of bizarre shape. Every fourth beat (R_4, R_8, R_{12}, and R_{16}) shows a narrower QRS complex and a deep S wave. It is preceded by a P wave at an interval of 0.22 second. These are ventricular fusion beats, which do not disturb the regularity of the tachycardia.

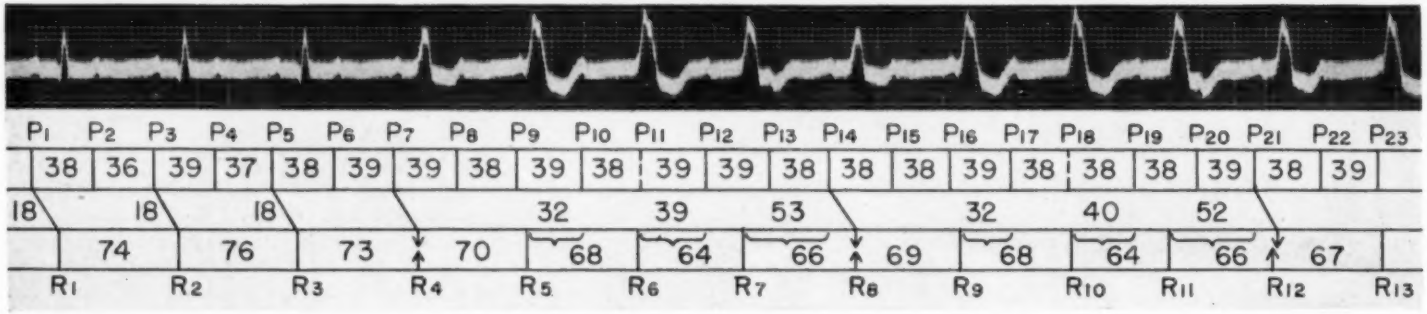

Fig. 4.—Lead II. A regular atrial tachycardia is present; rate, 158 per minute. Between P_1 and P_6 alternate atrial excitations are conducted to the ventricles. Then, at R_4, an ectopic ventricular rhythm sets in, characterized by bizarre ventricular complexes. The rate is 89 per minute. R_4, R_8, and R_{12} differ somewhat in shape and are narrower than the other QRS complexes of the ectopic ventricular rhythm. They are preceded by P waves at intervals of 0.14 to 0.16 second. The refractory period of the bundle is longer than the atrial cycle, which measures 0.39 second. P_{14} and P_{24} arrive late in the diastole when the bundle has recovered its conductivity; their R-P intervals are 0.53 and 0.52 seconds, respectively. These atrial excitations are conducted to the ventricles and cause ventricular fusion beats. P_7 produces, likewise, a ventricular fusion beat when it reaches the ventricles simultaneously with the onset of the ventricular tachycardia. (The figures in the diagram indicate 1/100 second.)

Fig. 2,*A* shows two strips of Lead II which form a continuous tracing. There is a perfectly regular tachycardia; the rate is 148 per minute. The bizarre shape of the ventricular complexes suggests ventricular origin of the tachycardia. The duration of QRS is 0.14 to 0.15 second. Signs of an independent atrial rhythm are not readily recognizable in the lower strip of the record. In the upper strip, some QRS complexes (R_5, R_8, R_{11}, and R_{14}) differ slightly in shape from the average beats; their duration is only 0.12 second, and their ascending limbs show a slur where the majority of the beats exhibit a distinct notch. These different QRS complexes are preceded by P waves which are superimposed as small, sharp peaks on the convexity of the T waves. The P-R intervals measure from 0.18 to 0.20 second. Obviously, the ventricular beats which follow these atrial waves are partly due to conducted sinus excitations, and represent ventricular fusion beats. It is noteworthy that the regularity of the ventricular action is not disturbed by the conducted sinus impulses. The bottom strip of the tachycardia shows neither regular P waves nor ventricular fusion beats. This is probably explained by a slight variation in the sinoauricular rate, which changes the time relations of the atrial excitations to the ventricular tachycardia. Fig. 2,*B*, (Lead II) shows sinus rhythm after cessation of the tachycardia. It can be noted that R_5, R_8, R_{11}, and R_{14} of the top strip are intermediate in shape between the sinoauricular beats and the bizarre complexes of the ventricular tachycardia.

Fig. 3 (Lead aV_F) presents another attack of ventricular tachycardia. The rate is 113 per minute. The duration of QRS is 0.18 second. The ventricular complexes are of bizarre shape. Every fourth beat, however, (R_4, R_8, R_{12}, and R_{16}) shows a slightly different QRS complex; its duration is only 0.12 second. These beats are preceded by P waves at intervals of 0.22 second. Obviously the ventricular systoles which differ in configuration from the majority of the beats are due to interference of conducted sinoauricular excitations with ventricular impulses. They represent ventricular fusion beats which do not disturb the regularity of the ventricular tachycardia.

Fig. 4 (Lead II) is an electrocardiogram of a 54-year-old man who suffered from hypertensive heart disease and congestive heart failure. He had received 1.3 Gm. of digitalis leaf within four days before the electrocardiogram was taken. The first part of the record shows a rapid atrial rhythm, rate of 158 per minute, with 2:1 atrioventricular block. The ventricular beats, R_1 to R_3, are of normal shape. Then (at R_4) an ectopic ventricular rhythm sets in which is fairly regular and has a rate of 89 per minute. The length of the ventricular cycles measures 0.64 to 0.70 second, that is, less than the double sinus period. The duration of QRS is 0.12 second. There are variations in the configuration of the ectopic ventricular beats which suggest that some atrial excitations may be conducted to the ventricles: R_4, R_8, and R_{12} are narrower and of smaller amplitude than the R waves of the majority of the ectopic ventricular beats. They are preceded by P waves at intervals measuring from 0.14 to 0.16 second. It can be noted that the fast atrial rhythm which was present in the first part of the record has persisted during the ectopic ventricular rhythm. Only alternate atrial excitations can be conducted to the ventricles. Hence, the refractory period of the bundle is longer than one atrial period, which measures 0.36 to 0.39 second. It may be assumed that the excitations of the ectopic ventricular rhythm, by penetrating into the junctional tissues in a retrograde way, render the bundle refractory.[5, 6] Those atrial excitations, which have an R-P interval that is longer than the refractory period of the bundle, can travel down the junctional tissues, and, if they arrive early enough, may activate at least part of the ventricles. This is true of P_{14} and P_{21}, whose R-P intervals are 0.53 and 0.52 seconds, respectively. These atrial excitations interfere in the ventricles with the simultaneously released ventricular impulses, and cause ventricular fusion beats (R_8 and R_{12}). P_7 also gives rise to a ventricular fusion beat as it arrives in the ventricles at the time of the onset of the ectopic ventricular rhythm. The other atrial excitations fall either too early in diastole, when the bundle is still refractory, or too late to reach the ventricles before they have been activated by the ectopic ventricular focus. The interplay of the two rhythms in the presence of 2:1 atrioventricular block results in dissociation with interference,[6] the latter being manifest in ventricular fusion beats. The regularity of the ectopic ventricular rhythm is not disturbed by the occasional conduction of atrial impulses. A toxic digitalis effect might have been responsible for both the atrial tachycardia and the ectopic ventricular rhythm.

Fig. 5 shows the electrocardiogram (Lead II) of a patient whose clinical data are not available. The top strip, *A*, presents a regular tachycardia; the rate is 136 per minute. The initial

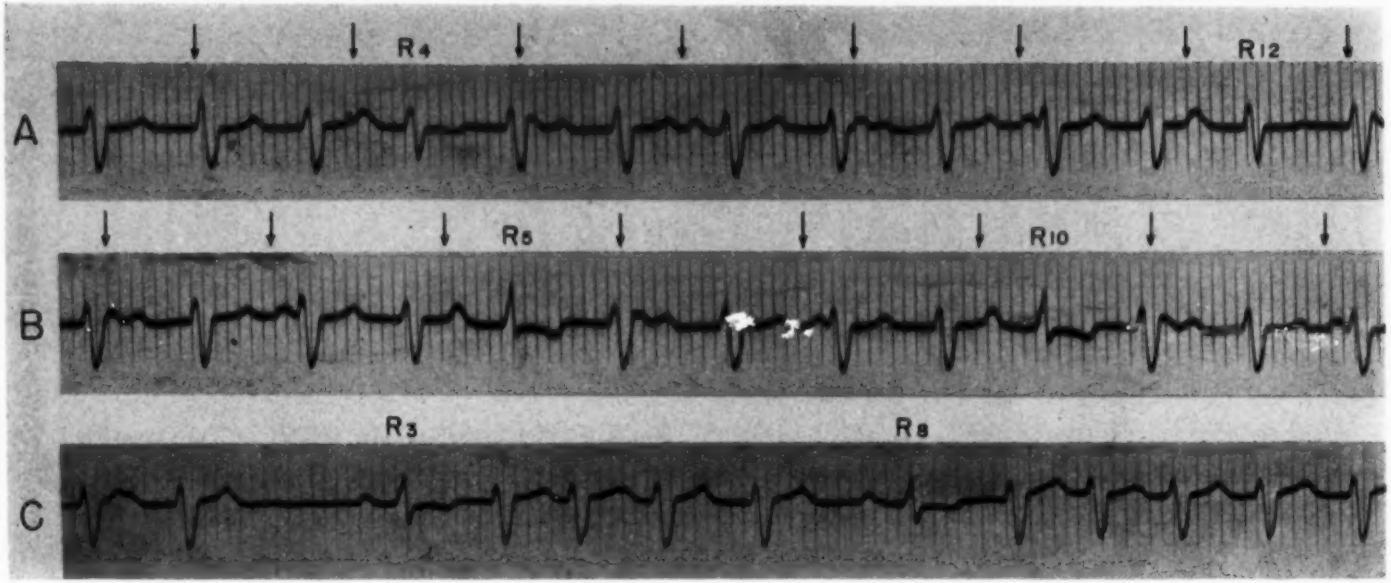

Fig. 5.—Lead II. *A*, Regular ventricular tachycardia; rate, 136 per minute. QRS is slurred; its duration is 0.10 second. An independent atrial rhythm (arrow) is present; its rate is 84 per minute. The fourth and twelfth ventricular beats differ somewhat in shape from the other systoles; the S wave is smaller, and the T wave is low and diphasic. These ventricular beats are preceded by P waves (arrow) at intervals of 0.16 and 0.19 seconds, respectively. Obviously conducted atrial excitations play a part in the formation of R_4 and R_{12}, which represent ventricular fusion beats. The regularity of the ventricular rhythm is not disturbed.

B, Another part of the same attack of tachycardia. The rate is unchanged. The fifth and tenth beats differ markedly in shape from the other systoles; they show prominent R deflections and inverted T waves. They are preceded by P waves which coincide with the T of the preceding ventricular beat. Obviously, R_5 and R_{10} are due to conduction of atrial impulses; they are quite similar in shape to R_3 and R_8 of the bottom strip.

C (of the same case) presents short runs of the same type of tachycardia as shown in *A* and *B*. The pauses after the bouts of tachycardia are concluded by sinoauricular beats (R_3 and R_8). (Time record 1/20 second.)

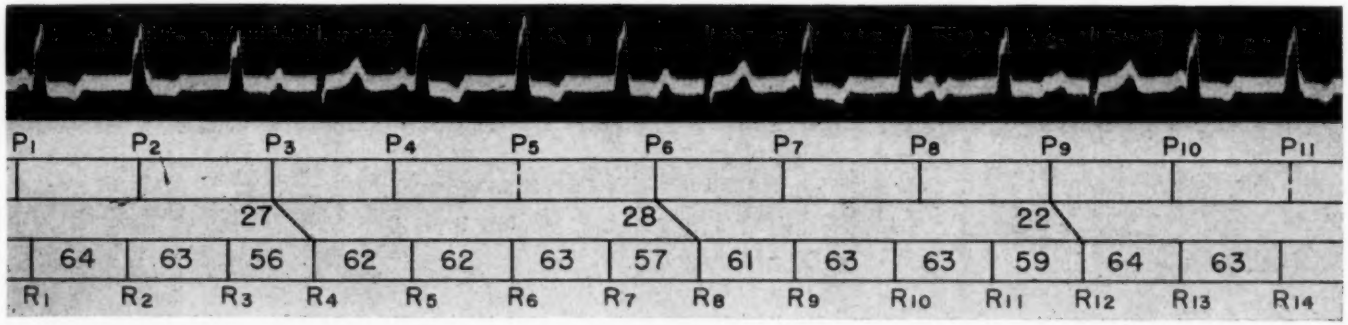

Fig. 6.—Lead I. A regular ventricular tachycardia is characterized by bizarre ventricular complexes; the rate is 95 per minute. An independent atrial rhythm is present; its rate is 75 per minute. The comparatively long ventricular cycles make it possible for a typical dissociation with interference to develop. Every third atrial excitation is conducted to the ventricles, and produces a premature beat of the supraventricular type (R_4, R_8, and R_{12}). The P-R interval of these beats varies from 0.22 to 0.28 second, depending on the time of incidence of the sinus impulse. The atrial excitation which arrives latest in diastole (P_9) has the shortest P-R interval. (The figures in the diagram indicate 1/100 second.)

ventricular complexes consist of small R and deep S waves, both of which are slurred. The duration of QRS is 0.10 second. The T waves are upright. The fourth and twelfth ventricular beats are somewhat different in shape; the S deflection is smaller, the duration of QRS is only 0.08 second, and the T wave is low and diphasic (minus-plus). An independent atrial rhythm with a rate of 84 per minute is easily recognizable. It is apparent that those atrial excitations which coincide with T are conducted to the ventricles and produce ventricular fusion beats (R_4 and R_{12}). R_4 has a P-R interval of approximately 0.19 seoond; R_{12} has a longer P-R interval (0.24 second), because the atrial excitation falls earlier in diastole when the junctional tissues are relatively refractory, and therefore requires a longer time to travel to the ventricles.

Fig. 5,*B* shows another part of the record taken during the same attack of tachycardia. The ventricular rate is again 136 per minute. R_5 and R_{10} are preceded by P waves which are fused with T; the P-R interval is 0.17 second. These beats, which are obviously caused by conducted atrial excitations, differ markedly from the average ventricular complexes. They show prominent R deflections and inverted T waves, bearing close resemblance to R_3 and R_8 of Fig. 5,*C*. The latter record was obtained on another occasion when the ventricular tachycardia occurred in short runs, interrupted by pauses during which sinoauricular beats (R_3 and R_8) occurred. It can be noted that in *A* and *B* the conducted sinoauricular excitations do not disturb the regularity of the tachycardia.

Fig. 6 is an electrocardiogram of a 21-year-old nurse who showed slight cardiac enlargement and hypertrophy of unknown etiology and good effort capacity. The electrocardiogram (Lead I) shows a ventricular tachycardia with a rate of 95 per minute. The length of the ventricular cycle is 0.62 to 0.64 second. The ventricular complexes are of bizarre shape. The duration of QRS is 0.09 to 0.10 second. An independent atrial rhythm, which is slower than the ventricular rhythm, is easily recognizable. Some ventricular beats (R_4, R_8, and R_{12}) are slightly premature, and their configuration suggests supraventricular origin. These beats are apparently produced by atrial excitations which either coincide with or follow closely the T waves of the preceding systoles. The P-R intervals of the conducted beats vary from 0.22 to 0.28 second, depending on the incidence of the atrial excitation. P_9, which falls later in diastole, has a shorter atrioventricular conduction time than the earlier occurring P_3 and P_6. In this case, because of the relatively long duration of the ventricular cycle, some atrial excitations can reach the ventricle early enough to produce premature beats of supraventricular configuration. This tracing presents a typical example of dissociation with interference.

COMMENT

In paroxysmal ventricular tachycardia, the ventricular excitations are only exceptionally conducted in a retrograde way to the atria.[7,8] Usually the atrial rhythm, which is slower than the ventricular rhythm, remains undisturbed. These conditions might be expected to lead to dissociation with interference.[9] That this arrhythmia develops only infrequently in the presence of paroxysmal ventricular tachycardia is due to the shortness of the ventricular cycle. In most instances the refractory period of the bundle plus the time required for the conduction of the atrial excitations to the ventricles is longer than the ventricular cycle; therefore, complete atrioventricular dissociation results. Only when the ventricular rate is less than 150 per minute can some of the atrial excitations which fall at a favorable time travel to the ventricles. In exceptional instances they produce premature beats of the supraventricular type, thus causing the typical picture of dissociation with interference (as in Fig. 6). More often the regularity of the ventricular rhythm is not disturbed, and interference manifests itself only in variations of the ventricular complex, which are intermediate in shape between the grossly abnormal beats of the ventricular tachycardia and sinoauricular beats. The finding of ventricular fusion beats may support a ques-

tionable diagnosis of paroxysmal ventricular tachycardia, when an independent atrial rhythm is not distinctly recognizable.

Reports in the literature on the occurrence of ventricular fusion beats in paroxysmal ventricular tachycardia are scant. An example of this type of dissociation with interference is published in the electrocardiographic text of Katz.[7] A report on paroxysmal ventricular tachycardia by Cooke and White[2] includes two tracings (Fig. 13, Case 21; and Fig. 1, Case 22) which show variations in the shape of the ventricular complexes apparently due to conduction of sinoauricular excitations. In discussing their Fig. 1, Case 22, the authors observe that ". . . breaks in the ventricular rhythm in Leads I and II are shown . . .," without commenting on the mechanism involved.

SUMMARY

Six instances of paroxysmal ventricular tachycardia are reported, which show variations of the ventricular complexes transitional in shape to sinoauricular beats. The variations are caused by transmission of atrial excitations to the ventricles, which mostly results in ventricular fusion beats. The regularity of the ventricular rhythm is only exceptionally disturbed by conduction of atrial excitations.

In the presence of paroxysmal ventricular tachycardia, dissociation with interference develops infrequently because of the shortness of the ventricular cycle. When it does occur, the ventricular rate is usually less than 150 per minute.

The finding of ventricular complexes which are transitional in configuration to sinoauricular beats may be an aid in the diagnosis of paroxysmal ventricular tachycardia when an independent atrial rhythm is not readily recognizable.

REFERENCES

1. Robinson, G. C., and Herrmann, G. R.: Paroxysmal Tachycardia of Ventricular Origin and Its Relation to Coronary Occlusion, Heart **8**:59, 1921.
2. Cooke, W. T., and White, P. D.: Paroxysmal Ventricular Tachycardia, Brit. Heart J. **5**:33, 1943.
3. Williams, C., and Ellis, L. B.: Ventricular Tachycardia, Arch. Int. Med. **71**:137, 1943.
4. Armbrust, C. A., and Levine, S. A.: Paroxysmal Ventricular Tachycardia: A Study of One Hundred and Seven Cases, Circulation **1**:28, 1950.
5. Langendorf, R.: Concealed A-V Conduction. The Effect of Blocked Impulses on the Formation and Conduction of Subsequent Impulses, Am. Heart J. **35**:542, 1948.
6. Dressler, W., and Roesler, H.: Dissociation With Interference in the Presence of 2:1 A-V Block, Am. Heart J. **44**:238, 1952.
7. Katz, L. N.: Electrocardiography (Figs. 328 and 322), Philadelphia, 1947, Lea & Febiger.
8. Grau, S., and Gouaux, J. L.: Paroxysmal Ventricular Tachycardia With Second Degree A-V Block and Reciprocal Rhythm, Circulation **2**:422, 1950.
9. Mobitz, W.: Zur Frage der atrioventriculaeren Automatie, Deutsches. Arch. f klin. Med. **141**:257, 1923.

THE T WAVE OF THE UNIPOLAR PRECORDIAL ELECTROCARDIOGRAM IN NORMAL ADULT NEGRO SUBJECTS

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THE T WAVE of the electrocardiogram is known to be one of the most variable components of the QRS-T complex. This wave is readily altered by physiologic factors, including temperature, changes in posture, digestive and neurological factors, as well as varied pathologic states. As yet, the exact mechanism of these changes is not fully understood.

A survey of the literature shows widely variable opinions concerning the limit and extent of T-wave changes in the normal precordial electrocardiogram. Much of this variation is due to differences in methods of recording the electrocardiogram especially in regard to the nature and location of the indifferent electrode. In spite of these differences in recording precordial leads there is considerable agreement in regard to T-wave inversion in these leads.

Most authors are agreed that the T wave in precordial electrocardiograms of adult subjects may be normally inverted over the right precordium, extending as far as the left sternal line in the fourth intercostal space.[1-5] T-wave inversion farther to the left of this line was almost never encountered by these authors in the precordial electrocardiograms of normal adult subjects.

On the other hand several authors have reported T-wave inversion in precordial leads over the left precordium as far as the midclavicular line, fifth intercostal space in Mexican,[6] Puerto Rican,[7] and Negro subjects,[8,9] who were said to be normal adults. If confirmed, these observations would be of considerable importance in the clinical management of patients of Mexican, Puerto Rican, and Negro stock.

MATERIALS AND METHODS

Eighty-five Negro subjects, forty-eight men and thirty-seven women, were selected for the study from the medical and nursing students at Howard University. These subjects ranged in age from 22 to 39 years. Careful histories were taken, and all individuals suspected of having previous cardiac disease or illness likely to result in cardiac abnormality were excluded from this series. Subjects with acute illnesses, such as upper respiratory infections, were also excluded.

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Received for publication May 19, 1952.

All electrocardiograms included in this series were taken by one of the authors using a Cambridge string galvanometer instrument run at a speed of 50 mm. per second. All tracings were taken with the subject lying down, after a rest period of at least fifteen minutes. Routine twelve-lead electrocardiograms were taken including Leads I, II, III, aV_R, aV_L, aV_F, and V_1 through V_6. In all the subjects selected, the conventional limb leads and unipolar limb leads were well within normal limits gauged by commonly accepted standards.

Complete analysis of the electrocardiograms were made, including statistical study of values obtained for the T waves in precordial leads. Measurement of axis deviation and electrical position of the heart was done according to commonly accepted normal standards.

RESULTS

Left axis deviation was found in seventeen subjects and normal axis in the remainder. The electrical position of the heart in these eighty-five subjects was: horizontal in eight, intermediate in thirty-nine, and vertical in thirty-eight.

The directions of the T wave in Leads V_1 through V_6 are tabulated in Table I. The T wave was upright from the V_3 position through V_6 in all eighty-five subjects. One of the eighty-five subjects, a 25-year-old woman, showed an inverted T wave in V_2. The direction of the T wave in V_1 was variable.

TABLE I

	V_1		V_2		V_3		V_4		V_5		V_6	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Inverted	29	34	1	1	0	0	0	0	0	0	0	0
Biphasic	8	10	0	0	0	0	0	0	0	0	0	0
Flat	3	3	0	0	0	0	0	0	0	0	0	0
Upright	45	53	84	99	85	100	85	100	85	100	85	100

Table II shows the magnitude as well as the direction of the T waves in the precordial leads. The maximum positive deflections of the T waves occurred in V_2, V_3, and V_4, and the maximum negative deflection of the T wave occurred in V_1.

DISCUSSION

Many studies[5, 10–15] have been presented showing that in children (below the age of 15) the T wave may be inverted in the precordial electrocardiogram as far to the left as the midclavicular line in the fifth intercostal space. This is an accepted normal variation in children, and the electrocardiographic pattern is generally known as the juvenile pattern. Various explanations have been offered for this phenomenon, the most common of which is that in the child there is rotation of the heart around its longitudinal axis in a clockwise direction allowing a greater portion of the right ventricle to occupy the left precordial area.[9] Other

TABLE II

LEADS	MINIMUM	MAXIMUM	MEAN	STANDARD DEVIATION
V_1	−4.0	+ 7.0	+1.0	±2.35
V_2	−0.5	+11.5	+5.0	±2.79
V_3	+1.5	+12.0	+5.6	±2.60
V_4	+1.0	+13.0	+5.5	±2.36
V_5	+1.0	+ 9.5	+4.5	±1.82
V_6	+0.5	+ 6.5	+3.3	±1.49

factors, including the relatively greater anterior-posterior diameter of the chest in children,[11] and the more intimate contact of the heart and the chest wall,[12] have also been offered in explanation. It has also been shown that from V_4 to V_1 negative T waves are progressively less frequent as the children get older.[15]

The persistence of a juvenile electrocardiographic pattern in adults has generally been interpreted as abnormal. Deeds and Barnes,[1] in the study of one hundred normal adults, found only one subject in whom the T wave approached negativity in CR_2. They concluded, therefore, that the juvenile pattern was abnormal in subjects older than 15 years. Stein,[2] in a study of 4,810 patients (both sexes, without evidence of organic heart disease) found inversion of the T wave in CR_4 in only twenty-three (0.48 per cent) of those examined. Following exercise these T waves became upright in all but one subject. Several studies have been made on the T waves in unipolar precordial V leads. The initial study by Kossman and Johnson[3] who surveyed thirty normal subjects using multiple unipolar leads reports no instance of an inverted T wave in V_2 or other leads taken farther to the left. An additional study[4] by Kossman, reported in 1950, of thirty-five normal individuals, shows no instance of T-wave inversion beyond the V_1 position.

Myers and associates[5] reporting on the electrocardiographic findings of fifty-two adult subjects, whose hearts were proved to be normal at autopsy, found T-wave inversion in V_2 in three individuals. These three individuals were women and constituted a total of 12 per cent of the female hearts examined. Two of these subjects with inverted T waves in V_2 were Negroes. He concluded these changes represented normal variation.

Suarez and Suarez,[7] in a study of eighty-one adult Puerto Rican men and women between the ages of 19 and 46, concluded that a negative T wave in V_2, V_3, V_4, V_5, and V_6 was probably abnormal, especially in the last four. However, 10 per cent of the men in his study had flat or diphasic T waves in V_2. In the adult women, he found that the T waves may be negative in V_1, V_2, and V_3, but not in V_4, V_5, and V_6. Of the women, 22.5 per cent had abnormal T waves (inverted, flat, or diphasic) in V_2, and 9 per cent had abnormal T waves in V_3.

Littman[8] reported an incidence of abnormal (inverted, diphasic, or flat) T waves in CF_4 in 4.66 per cent of 300 normal Negro subjects. In one hundred normal Negro women, he reported a similar change in CF_4 in 8 per cent. This was compared to an incidence of 0.5 per cent abnormal T waves in a similar study involving 200 white subjects. He concluded, therefore, that T-wave inversion in CF_4 is more common in the normal Negro subjects, and is seen more frequently in Negro women than in Negro men.

We are not certain as to the significance of these observations. If all of the adults in this study were really normal subjects, it is obvious that different standards of T-wave inversion in precordial leads would have to be used for white and Negro subjects. No effort was made in our study to confirm this report with CF leads, since the unipolar precordial V leads are now more widely used.

In the study of 500 normal Mexicans, Vaquero and associates[6] conclude that normal adults may have T-wave inversion as far left as V_4, but it is exceptional to find such changes in V_5. In this study, they found V_2 to be negative in 14.7 per cent of individuals above the age of 20. V_3 was negative in 0.8 per cent in individuals over 20.

The significance of the inverted T waves to the left of V_2 observed in a considerable number of Mexican and Puerto Rican subjects is uncertain. Additional studies in these groups should be reported.

The data from our study fails to confirm the statement by Goldberger[9] that persistent T-wave inversion in precordial electrocardiograms to the left of V_2 is a common finding in normal Negro adults. The T-wave patterns in the eighty-five normal Negro subjects reported here indicate no significant deviation from the existing standards as reported by Kossman and Johnson[3,4] and Meyers and associates.[5]

SUMMARY AND CONCLUSIONS

1. A review of the literature is presented in which it appears that the T wave in precordial electrocardiograms of normal adult subjects may be inverted over the right precordium extending as far as the left sternal line. Persistence of T-wave inversion farther to the left is generally considered abnormal.

2. In contrast, others have reported T-wave inversion over the left precordium as far as the left midclavicular line in Mexican, Negro, and Puerto Rican adults who were said to be normal subjects.

3. A study of the T wave in unipolar precordial electrocardiograms of eighty-five normal adult Negro subjects has been presented which confirms the standard generally accepted for normal adults.

4. In this series of normal adults, no instance of T-wave inversion was found to the left of the V_2 position, and in only one instance was an inverted T wave found in V_2.

REFERENCES

1. Deeds, D., and Barnes, A. R.: The Characteristics of the Chest Lead Electrocardiograms of 100 Normal Adults, AM. HEART J. **20**:261, 1940.
2. Stein, I.: A Study of Abnormal T Waves in Patients Presenting No Evidence of Organic Heart Disease, J. Lab. & Clin. Med. **31**:837, 1946.
3. Kossman, C. E., and Johnson, F. D.: Precordial Electrocardiogram; Potential Variations of Precordium and of Extremities in Normal Subjects, AM. HEART J. **10**:925, 1935.
4. Kossman, C. E.: Interpretation of Unipolar Precordial Electrocardiograms, M. Clin. North America **34**:833, 1950.
5. Myers, G. B., Klein, H. A., Stoffer, B. E., and Hiratzka, T.: Normal Variations in Multiple Precordial Leads, AM. HEART J. **34**:785, 1947.
6. Vaquero, M., Limson-Lason, R., and Limson-Lason, A.: Electrocardiogram Normal. Estudio de 500 Casos en derivaciones Standard y Unipolares, Arch. inst. cardiol. Mexico **17**:155-168, 1947.
7. Suarez, R. M., and Suarez, R. M., Jr.: The T Wave of the Precordial Electrocardiogram at Different Age Levels, AM. HEART J. **32**:480, 1946.
8. Littman, D.: Persistence of the Juvenile Pattern in the Precordial Leads of Healthy Adult Negroes, With Report of Electrocardiographic Survey in 300 Negroes and 200 White Subjects, AM. HEART J. **32**:370, 1946.
9. Goldberger, E.: Unipolar Lead Electrocardiography, Philadelphia, 1947, Lea & Febiger.
10. Goldberger, E.: The Significance of Downward T Waves in Precordial Leads of Normal Children, Am. J. Dis. Child. **71**:518, 1946.
11. Master, A. M., Dack, S., and Jaffee, H. L.: The Precordial Electrocardiogram of Normal Children, Am. J. Dis. Child. **53**:1000, 1937.
12. Robinow, M., Katz, L. N., and Bohning, A.: The Appearance of the T Wave in Normal Children and in Children With Rheumatic Heart Disease, AM. HEART J. **12**:88, 1936.
13. Kuskin, L., and Brockman, L.: The Direction of the Precordial T Wave in 321 Normal Infants and Children, Am. J. M. Sc. **218**:55, 1949.
14. Littman, D.: Juvenile Electrocardiogram, Am. J. Med. **3**:526, 1947.
15. Yu, P. N., Joos, H. A., and Katsampes, C. P.: Unipolar Electrocardiogram in Normal Infants and Children, AM. HEART J. **41**:91, 1951.

AURICULAR FIBRILLATION

Hemodynamic Studies Before and After Conversion with Quinidine*

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IN RECENT years, there has been a revival of interest concerning the desirability of converting long-standing auricular fibrillation to regular sinus rhythm.[1,2] The use of quinidine to restore sinus rhythm in chronic fibrillation in association with severe heart disease has been considered to be contraindicated,[3] especially in those patients whose ventricular rate has been kept slow by adequate digitalization.[4] The danger of embolism upon restoration of regular rhythm and the fear of cardiac arrest have been prime factors in perpetuating this opinion. However, little attention has been paid to the hemodynamic alterations that follow the change from auricular fibrillation to sinus rhythm, and a comprehensive perusal of available literature prior to 1950 revealed no systematic study of these hemodynamic changes by the method of right heart catheterization.

The present study was undertaken in an effort to determine the influence of this arrhythmia upon cardiovascular mechanics as determined by the method of right heart catheterization, using a modification of the dye injection technique.

CLINICAL MATERIAL

The fourteen patients studied in this series were regular visitors to the Heart Clinic of the Louisville General Hospital. The duration of observation prior to the beginning of this study varied from six months to five years. An accurate record of previous treatment was obtained on each patient. Every patient with chronic auricular fibrillation who was seen by the authors was selected for prospective hemodynamic studies; those whose congestive failure could not be satisfactorily controlled by routine methods were later eliminated from the group. No patient was excluded simply because of the severity or the etiological classification of his heart disease, the duration of the atrial fibrillation, or his heart size. Willingness to submit to repeated cardiac catheterizations and absence of frank congestive failure at the time were the only requisites.

Every patient in the entire group was maintained on digitalis therapy. Low salt intake, ammonium chloride, mercurial diuretics, etc., were given as clinically

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Received for publication June 6, 1952.

*This work supported in substance by the National Heart Research Grant #H-1140.

Preliminary report.

Technical assistance by Mrs. Dorothy Klune Anderson.

indicated, before and during the observation period. All patients remained on outpatient status and were followed in the clinic.

The venous pressure[5] was elevated in only two patients prior to the initial catheterization, although the mean circulation time was prolonged in all but one. None had peripheral edema or ascites at the time of study. All clinical resources except quinidine were used to maintain the best possible state of cardiac compensation and well-controlled ventricular rates.

METHODS

Right heart catheterization was carried out after the method of Cournand and Ranges.[6] Whenever possible the catheter was advanced to the bifurcation of the pulmonary artery. Cardiac output was determined by the dye injection method of Moore, Kinsman, Hamilton, and Spurling,[7] the dye being injected through the intracardiac catheter. Right atrial, pulmonary arterial, and radial arterial pressures were measured and recorded by the Sanborn electromanometer, mean pressures being determined by electrical integration of the pressure tracings. Intracardiac pressure tracings were recorded in many instances. Control studies included: cardiac output, pulmonary blood volume,[8] right atrial pressure, pulmonary and radial arterial pressures, venous pressure, vital capacity, mean circulation time, and total blood volume. Heart rate was determined from electrocardiographic tracings. Total peripheral resistance was calculated from the following formula[9]:

$$R = \frac{Pm \times 1332}{CO}$$

Pm = mean radial artery pressure and 1332 is a constant. CO represents cardiac output in c.c./second, and the product is expressed as dynes $cm.^{-5}$ second (absolute unit).

Control studies were obtained with the patient supine after the catheter had been in position for fifteen minutes. Following the control observations the patient exercised[10] for twelve minutes while in the supine position. Exercise consisted of lifting a 20-pound weight alternately with each foot over a distance of twelve inches at a uniform rate, using pulley connections whereby horizontal pressure on the foot pedal produced vertical elevation of the weight. No measurement of actual work load was attempted. Twelve of the fourteen patients were able to tolerate the full exercise period, one was unable to tolerate any exercise.

The studies were repeated immediately following the exercise and again twenty minutes later after a rest period. The patient remained supine at all times. Undue apprehension was allayed by 0.1 to 0.2 Gm. of Seconal. The venous and arterial cutdowns were done under 2 per cent procaine local anesthesia. No other medication was administered at the time of the procedure.

Upon completion of these initial studies, the patients were started on quinidine sulfate. After the customary test dose of 0.2 Gm., the drug was given three to four times daily, the dose being increased every fourth day until either conversion to a normal sinus rhythm, marked electrocardiographic alterations, or patient intolerance was observed. When conversion to a sinus rhythm was

verified electrocardiographically, the amount of quinidine was gradually reduced to a daily level necessary to maintain a sinus rhythm. This varied from 0.6 to 3.2 Gm. with an average of approximately 1.4 Gm. daily. Electrocardiograms were checked at frequent intervals and after maintenance of a sinus rhythm for from three weeks to two months the above studies were repeated.

RESULTS

This paper is concerned with the findings in the fourteen patients in whom adequate studies were completed while the atria were fibrillating and again following resumption of a normal sinus rhythm under quinidine. Those patients failing to convert to a sinus rhythm and those with frank congestive failure are the subject of additional investigation. The changes in pulmonary blood volume,

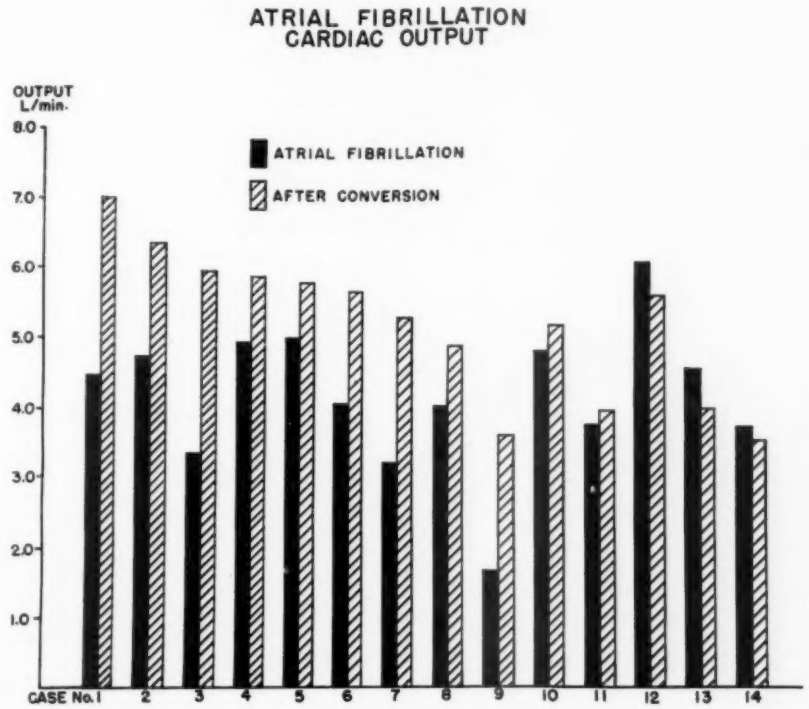

Fig. 1.

peripheral resistance, radial arterial pressure, right atrial pressure, pulmonary arterial pressure, and venous pressure produced by exercise in this group were not essentially different when the response during atrial fibrillation was compared to the response after conversion. The exercise response in these categories, therefore, will not be discussed but investigation is being pursued.

CARDIAC OUTPUT

In order to evaluate the changes observed, control data[11] from this laboratory were analyzed to determine the range of variation expected with the technique

employed. It was concluded that any cardiac output change greater than 10 per cent from the initial value could be considered significant. The resting output in normal individuals using the dye injection technique has been found to vary between 3.2[11] and 3.93[12] L./min./M², and the normal cardiac index using the Fick principle varies from 3.12[13] to 4.07[14] L./min./M² (Fig. 1).

Resting.—In fourteen patients the cardiac output was determined in a resting state before and after conversion. The resting output in all subjects expressed as cardiac index was lower during atrial fibrillation than the output found by similar methods in normal patients,[12] the cardiac indices varying from 1.08 to 2.81 L./min./M² (Table I). There was a significant increase in resting output after conversion in nine patients, although in only six of these did the output rise to a normal resting level. Five patients showed no significant change following restoration of sinus rhythm.

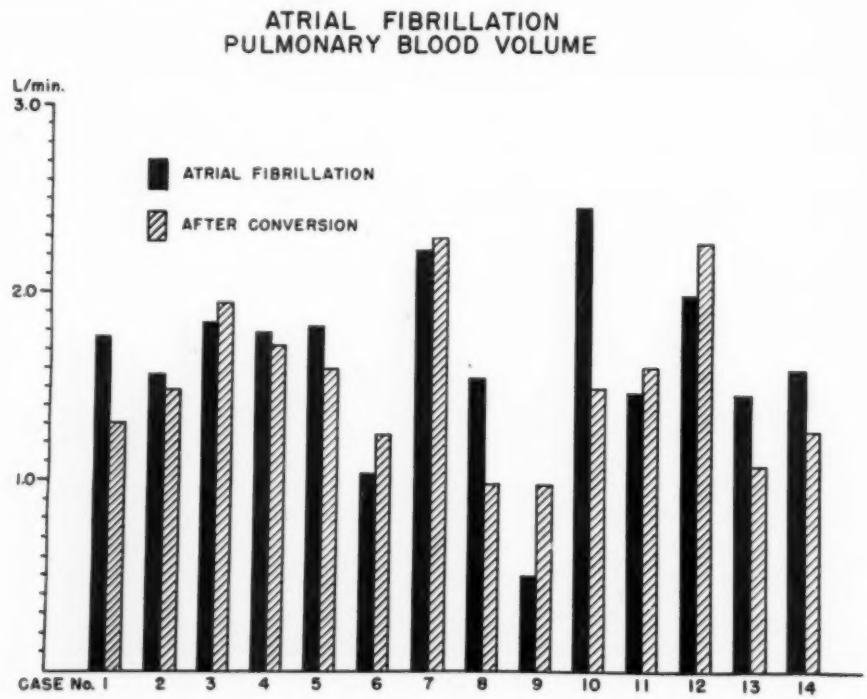

Fig. 2.

Exercise Response.—Five of the twelve patients who were exercised for the full period while fibrillating showed a significant increase in cardiac output over the resting value in response to the standard exercise, the increase being 41.8, 31.3, 29.7, 17.4, and 16.2 per cent, respectively, with an average increase of 27.3 per cent. In one patient the output fell 13.5 per cent following the exercise. In four there was an increase and in two a decrease in output, but not beyond the range of technical error and, therefore, considered not significant. The average rise in cardiac output was 17.9 per cent in the nine patients who showed an increase over the resting value.

TABLE I

CASE	CONDITION	PERIOD	CARDIAC OUTPUT	PERIPHERAL RESISTANCE	PULMONARY BLOOD VOLUME	CARDIAC INDEX	BLOOD VOLUME
1.	Atrial fibrillation	Control	4454	1507	1767	2.34	
		Exercise	6317	1139	1984	3.32	
		Post exercise	3925	1711	1609	2.06	
	Sinus	Control	6850	870	1393	3.65	
		Exercise	8255	836	1582	4.40	
		Post exercise	7142	1085	1857	3.81	
2.	Atrial fibrillation	Control	4698	2041	1550	2.51	6002
		Exercise	4427	2165	1402	2.31	
		Post exercise	3482	2525	1242	1.86	
	Sinus	Control	6268	1459	1494	3.55	6045
		Exercise	7145	1400	1751	3.82	
		Post exercise	5535	1661	1439	2.96	
3.	Atrial fibrillation	Control	3374	2868	1844	1.77	
		Exercise	3414	3043	1645	1.79	
		Post exercise	3035	3318	1502	1.57	
	Sinus	Control	5980	1207	1634	3.5	7486
		Exercise	7461	1182	1666	3.9	
		Post exercise	8742	914	2215	4.6	
4.	Atrial fibrillation	Control	4923	1916	1789	2.81	
		Exercise	4652	2268	1783	2.65	
		Post exercise	4005	2674	1556	2.29	
	Sinus	Control	5874	1361	1713	3.33	
		Exercise	6052	1460	1687	3.44	
		Post exercise	4914	1789	1572	2.79	
5.	Atrial fibrillation	Control	4950	2099	1815	2.53	
		Exercise	5754	1875	2167	2.91	
		Post exercise	5307	2423	2264	2.72	6797
	Sinus	Control	5709	1889	1599	2.91	
		Exercise	6188	1744	2258	3.15	11871
		Post exercise	4306	2415	1687	2.13	

TABLE I—(CONT'D)

CASE	CONDITION	PERIOD	CARDIAC OUTPUT	PERIPHERAL RESISTANCE	PULMONARY BLOOD VOLUME	CARDIAC INDEX	BLOOD VOLUME
6.	Atrial fibrillation	Control	4017	2089	1004	2.66	
		Exercise	4789	2349	944	3.19	
		Post exercise	4302	2321	975	2.85	5180
	Sinus	Control	5610	1852	1244	3.95	5478
		Exercise	5552	2006	1212	3.91	
		Post exercise	4448	2336	1045	3.13	
7.	Atrial fibrillation	Control	3192	3353	2224	1.9	
		Exercise	4190	2808	3073	2.5	
		Post exercise	3373	3175	2277	2.0	
	Sinus	Control	5224	1607	2281	3.11	5980
		Exercise	5453	1464	2236	3.24	
		Post exercise	4397	1904	1943	2.61	
8.	Atrial fibrillation	Control	4010	2790	1537	2.07	
		Exercise					
		Post exercise					
	Sinus	Control	4840	1273	1016	1.9	4231
		Exercise					
		Post exercise					
9.	Atrial fibrillation	Control	1613	5168	495	1.08	
		Exercise	1721	5012	442	1.16	
		Post exercise	1415	6096	432	0.95	
	Sinus	Control	3564	1974	962	2.44	
		Exercise	3715	2324	892	2.54	
		Post exercise	2207	2758	721	1.51	
10.	Atrial fibrillation	Control	4778	1388	2437	2.77	5861
		Exercise	5115	1375	2200	2.97	
		Post exercise	5097	1322	2526	2.92	
	Sinus	Control	5166	1469	1464	2.93	6301
		Exercise	6155	1298	1500	3.49	
		Post exercise	6003	1532	1691	3.41	

TABLE I—(CONT'D)

CASE	CONDITION	PERIOD	CARDIAC OUTPUT	PERIPHERAL RESISTANCE	PULMONARY BLOOD VOLUME	CARDIAC INDEX	BLOOD VOLUME
11.	Atrial fibrillation	Control	3773	1821	1289	2.54	5807
		Exercise	3264	2547	1219	2.22	
		Post exercise	3815	2032	1386	2.59	
	Sinus	Control	3685	2302	1314	2.82	6434
		Exercise	4507	2217	1487	3.04	
		Post exercise	4255	2254	1532	2.87	
12.	Atrial fibrillation	Control	6016	1132	1986	2.68	8237
		Exercise	7800	1125	2089	3.48	
		Post exercise	5019	1306	1737	2.24	
	Sinus	Control	5478	1312	2264	2.47	5899
		Exercise	6978	1031	2256	3.14	
		Post exercise	4800	1166	1920	2.16	
13.	Atrial fibrillation	Control	4513	1639	1319	2.78	4758
		Exercise	4932	1215	1554	3.04	
		Post exercise	3920	1733	1241	2.42	
	Sinus	Control	3956	2425	1068	2.41	4713
		Exercise	5487	1676	1344	3.35	
		Post exercise	3868	2271	1019	2.35	
14.	Atrial fibrillation	Control	3694		1588	2.73	
		Exercise					
		Post exercise					
	Sinus	Control	3509	1731	1240	2.61	5822
		Exercise					
		Post exercise					

Following conversion to and maintenance of a normal sinus rhythm seven of the twelve patients showed significant increase in cardiac output following exercise, the figures being 38.7, 27.4, 24.8, 20.5, 19.1, 16.0, and 14.0 per cent, with an average rise of 22.9 per cent. Four showed a slight increase and one a slight

decrease following exercise but these changes were not considered significant. The latter patient had responded to exercise while fibrillating by a significant increase in output.

Recovery.—Twenty minutes after completion of the exercise, recovery studies were done. While the patients were fibrillating there was a fall to values below the initial resting level in seven, the final value in each case being greater than 10 per cent below the resting value, with the average being 15.5 per cent. In five patients the recovery value was greater than that for the control period, but in no case was the increase greater than 7 per cent, and, therefore, these changes

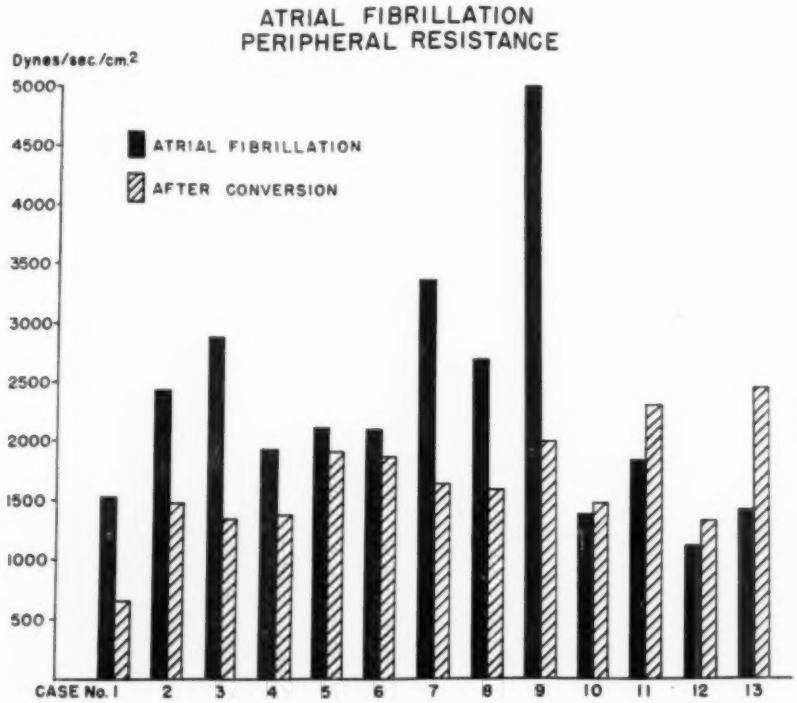

FIG. 3.

are considered not significant. Following the restoration of sinus rhythm, eight patients had outputs at the recovery time which had decreased to values below the initial resting level. The average fall was 16.2 per cent from the resting value with variation from 2.2 per cent to 38.1 per cent. Of these eight patients, however, only six showed changes of sufficient magnitude to exceed the expected technical variation. The recovery output was increased over the resting level in four patients, the figures being 4.3, 46.2, 6.2, and 9.5 per cent, respectively.

PULMONARY BLOOD VOLUME

The volume of circulating blood in the pulmonary vessels, left heart, aorta, and certain of the larger systemic vessels, calculated after the method of Stewart,[8]

is designated pulmonary blood volume (Fig. 2). In some patients in this group, the dye was injected into the right atrium or ventricle and the calculated volume would therefore include the volume of the right heart. In the majority of patients, however, the dye was injected into the pulmonary artery.

The values for pulmonary blood volume varied from 500 to 2,437 c.c. with a mean value of 1,627 c.c. in the fourteen patients during fibrillation (Table I). After restoration of a sinus rhythm the pulmonary blood volume varied from 960 to 2,280 c.c. with a mean value of 1,453 c.c. In seven patients in whom the total blood volume was determined while fibrillating, the pulmonary blood volume averaged 28.3 per cent of the total volume; while after conversion the pulmonary blood volume averaged 23.4 per cent of total blood volume.

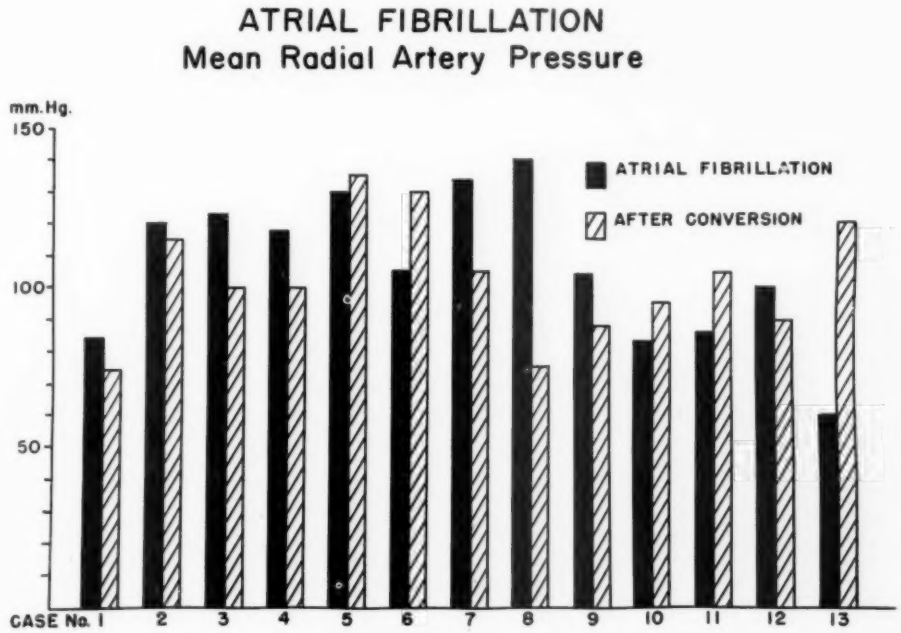

Fig. 4.

PERIPHERAL RESISTANCE

The normal value for peripheral resistance as determined by this method was considered to lie between 600 and 2,000 units (Fig. 3). This value was determined in thirteen patients during fibrillation and after conversion. In seven patients, peripheral resistance was elevated above the normal value at the initial examination (Table I). All the subjects were on maintenance doses of quinidine at the time the second catheterization procedure was done and at this time only two patients showed values above the normal range. Regardless of the value determined at the initial study nine of the patients showed a significant fall in peripheral resistance at the time of the subsequent study.

TABLE II

CASE	CONDITION		HEART RATE	MEAN RIGHT ATRIAL PRESSURE	MEAN PULMONARY ARTERIAL PRESSURE	RIGHT VENTRICULAR PRESSURE	VITAL CAPACITY	MEAN CIRCULATION TIME	BLOOD PRESSURE	MEAN RADIAL ARTERIAL PRESSURE
1.		a	64	6		86	71	23.8	112/74	84
		b	100	7				18.8		90
	Atrial fibrillation	c	77	5				24.6		84
		a	75	1	29	162	78	17.4	130/70	74.5
		b	78		22			11.5		86
	Sinus	c	76		10			15.5		94.5
2.		a	60	9	33	136	68	19.8	188/106	120
		b	62		32			19.0		120
	Atrial fibrillation	c	60	9	25			21.4		116
		a	62	2	20	46	73	14.3	190/100	114
		b	64		23			14.7		125
	Sinus	c	60	2	21			15.6		115
3.		a	80			100	65	32.8	105/100	122
		b	130					28.7		130
	Atrial fibrillation	c	95					29.7		126
		a	56	5	20	100	69	19.4	160/100	100
		b	64		27			13.4		110
	Sinus	c	60		20			15.2		100
4.		a	96			100		21.8	172/96	118
		b	106					23.0		132
	Atrial fibrillation	c	94					23.3		134
		a	72			34		17.5	175/90	100
		b	80					16.7		110
	Sinus	c	68					19.2		110
5.		a	70	4	24	92	74	22.0	166/116	130
		b	80		26			22.6		135
	Atrial fibrillation	c	80		28			25.6		161
		a	62	2	22	74	70	16.8	190/108	135
		b	80		27			21.9		135
	Sinus	c	65		23			23.5		135

6.		a	74	2	20	140	68	15.0	210/100	105
		b	80		18			11.8		141
	Atrial fibrillation	c	72		18			13.6		125
		a	58	3	18	160	69	13.3	235/100	130
		b	62		18			13.1		140
	Sinus	c	54		16			14.1		130
7.		a	84			57	74	41.8	170/90	134
		b	104					44.0		148
	Atrial fibrillation	c	86					40.5		134
		a	68		17	95	75	26.2	175/90	105
		b	96					24.6		100
	Sinus	c	64					27.2		105
8.		a	60			107	78	23.0	150/105	140
		b								
	Atrial fibrillation	c								
		a	64			40	41	15.8	108/68	73
		b								
	Sinus	c								
9.		a	75			96	73	18.4	137/74	104
		b	96					15.4		108
	Atrial fibrillation	c	80					17.6		108
		a	77			90	58	16.2	124/74	88
		b	70					14.4		108
	Sinus	c	64					19.6		76
10.		a	64			100	74	30.6	134/66	83
		b	40					25.8		88
	Atrial fibrillation	c	75					30.2		83
		a	58			98	68	17.0	134/60	95
		b	62					14.6		100
	Sinus	c	58					16.9		115
11.		a	68	7	26	140	54	20.5	160/85	86
		b	80		21			22.4		104
	Atrial fibrillation	c	80		33			21.8		97
		a	100	5	50	108	54	20.3	148/94	112
		b	100		56			19.8		125
	Sinus	c	100		42			21.6		120

TABLE II—(CONT'D)

CASE	CONDITION		HEART RATE	MEAN RIGHT ATRIAL PRESSURE	MEAN PULMONARY ARTERIAL PRESSURE	RIGHT VENTRICULAR PRESSURE	VITAL CAPACITY	MEAN CIRCULATION TIME	BLOOD PRESSURE	MEAN RADIAL ARTERIAL PRESSURE
12.		a	90		25	172	102	19.8		100
		b	100		30			16.2		100
	Atrial fibrillation	c	90		25			20.8		110
		a	65		12	94	98	24.8		90
		b	80		12			19.4		90
	Sinus	c	70		10			24.0		70
13.		a	60	1	8	76	56	19.4	118/80	80
		b	70		9			18.9		75
	Atrial fibrillation	c	68		8			19.0		85
		a	54	8	37.5	117	58	16.2		120
		b	60		35			14.7		115
	Sinus	c	60		33			15.8		110
14.		a	70			140	52	25.8		
		b								
	Atrial fibrillation	c								
		a	68	7		104	39	21.2		76
		b								
	Sinus	c								

a = resting
b = exercise
c = recovery

MEAN RADIAL ARTERIAL PRESSURE

The average control variation in mean radial arterial pressure with our technique was 5 mm. Hg, with a maximum pressure variation of 10 mm. Hg (Fig. 4).

The mean radial arterial pressure was determined in thirteen patients (Table II). As some of these patients were hypertensive and some were normotensive there was no consistency regarding the resting mean arterial pressures among the group. Compared to the resting pressure during fibrillation eight of these subjects showed a fall in mean radial artery pressure when they were studied with a sinus rhythm. The average fall in mean pressure in these eight patients was 22.1 mm. Hg. The remaining five patients showed a rise in mean radial artery pressure at the second study with an average 21.6 mm. Hg elevation over the level when fibrillating.

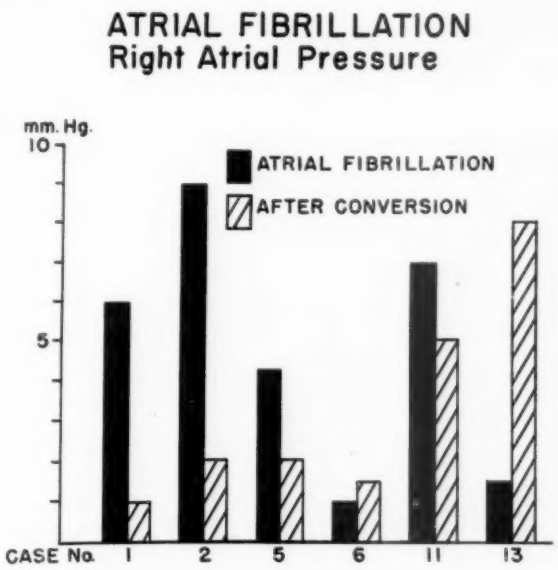

Fig. 5.

MEAN RIGHT ATRIAL PRESSURE

Any persistent change in mean right atrial pressure was felt to be significant. Right atrial pressure was determined in six patients before and after restoration of a regular rhythm (Table II). In four patients there was a fall in mean right atrial pressure averaging 4 mm. Hg with the return of regular rhythm. There was an increase in right atrial pressure following conversion in one and no change in right atrial pressure in the other patient (Fig. 5).

MEAN PULMONARY ARTERIAL PRESSURE

The average control variation in mean pulmonary arterial pressure with our technique was 2 mm. Hg with a maximum deviation of 5 mm. Hg. This measurement was taken in six patients (Table II). Following conversion there was a fall

in mean pulmonary arterial pressure in four patients of 13, 13, 2 and 2 mm. Hg as compared to the resting level while fibrillating, and there was an increase in pulmonary arterial pressure of 25 mm. Hg in two patients following restoration of sinus rhythm (Fig. 6).

VENOUS PRESSURE

After conversion to a sinus rhythm the venous pressure (Table II) was lower in nine of the fourteen patients tested as compared to pressure taken during atrial fibrillation. The average fall in venous pressure was 44 mm. H_2O with values ranging from 2 mm. to 90 mm. H_2O. In four patients the venous pressure as determined during sinus rhythm was higher than the resting level during fibrillation with increases of 76, 20, 38, and 41 mm. H_2O and an average rise of 44 mm. H_2O. As mentioned above, in only two patients was there abnormal elevation of venous pressure at the initial determination while atrial fibrillation was present (Fig. 7).

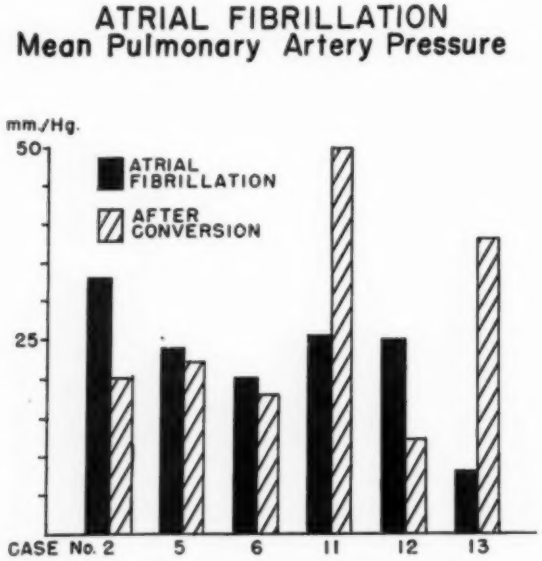

Fig. 6.

VITAL CAPACITY

There was no consistent change in this measurement when comparison was made between the capacity while fibrillating and the capacity after conversion to sinus rhythm.

MEAN CIRCULATION TIME

In thirteen there was an increase in the rate of blood flow following conversion, as determined by mean circulation time values. In only one patient was the circulation time longer following restoration of sinus rhythm than that determined during the period of atrial fibrillation; however, in this patient at the time of the second study, the dye was injected into the right ventricle as com-

pared to a pulmonary artery injection in the initial study. The data on this patient are, therefore, not comparable. The average mean circulation time of all fourteen patients during fibrillation was twenty-four seconds, whereas during sinus rhythm the circulation time averaged 18.6 seconds (Fig. 8).

HEART RATE

As emphasized above, all patients were well maintained on digitalis throughout the entire period of observation. At the time of initial study the ventricular rate varied between 60 and 90 with an average of 72 beats per minute, in the fourteen patients. While maintaining a sinus rhythm, rates varied between 54 and 100 with an average of 66 beats per minute.

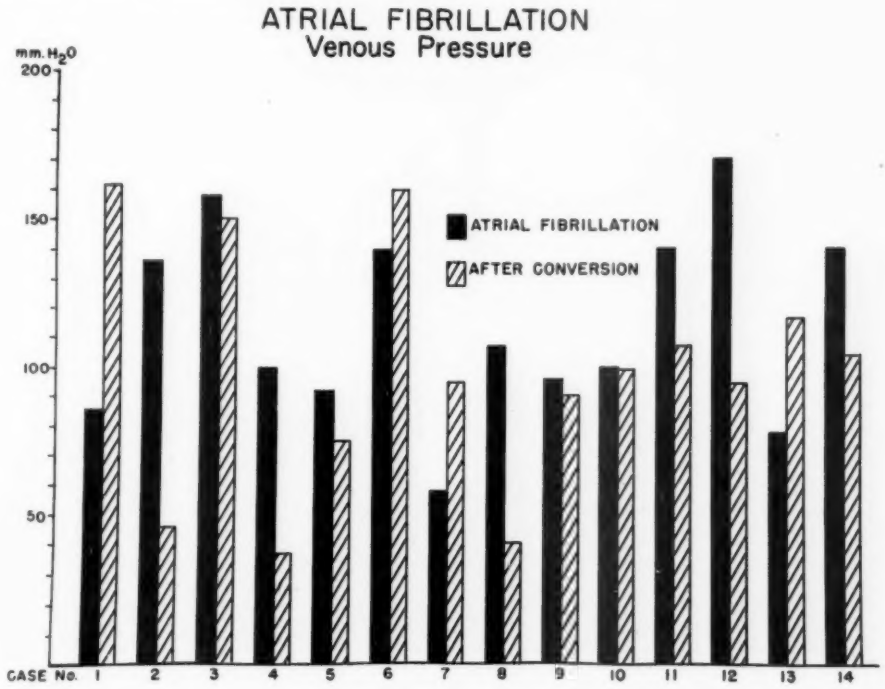

Fig. 7.

DISCUSSION

It seems apparent from the changes noted in this group of patients that the re-establishment of sinus rhythm was beneficial in the majority. The entire group showed a definite improvement in many of their cardiocirculatory functions; however, in only nine of these patients was this improvement evidenced by an increase in cardiac output. The cardiac index was below the accepted normal in the entire group during fibrillation and within normal limits in only two patients following restoration of sinus rhythm. This fact is not surprising in view of the severity and long duration of their cardiovascular disease. It is interesting to note that in Case 14 there was no increase in output after conversion. This

patient had a severe mitral stenosis and it was thought that the size of the mitral valve may have offered an impediment to further increase in ventricular filling. Case 1, a patient with mitral insufficiency, showed the greatest increase in cardiac output upon restoration of sinus rhythm. Since all of these patients had well-controlled ventricular rates which did not appreciably change upon restoration of sinus rhythm, the increase in output cannot be attributed to a change in ventricular rate. Restoration of sinus rhythm improved the exercise response in eight of the twelve patients able to tolerate this procedure. The amount of exercise was considerable in view of the severity of the heart disease and the increase in exercise tolerance probably represents a considerable improvement in cardiocirculatory function.

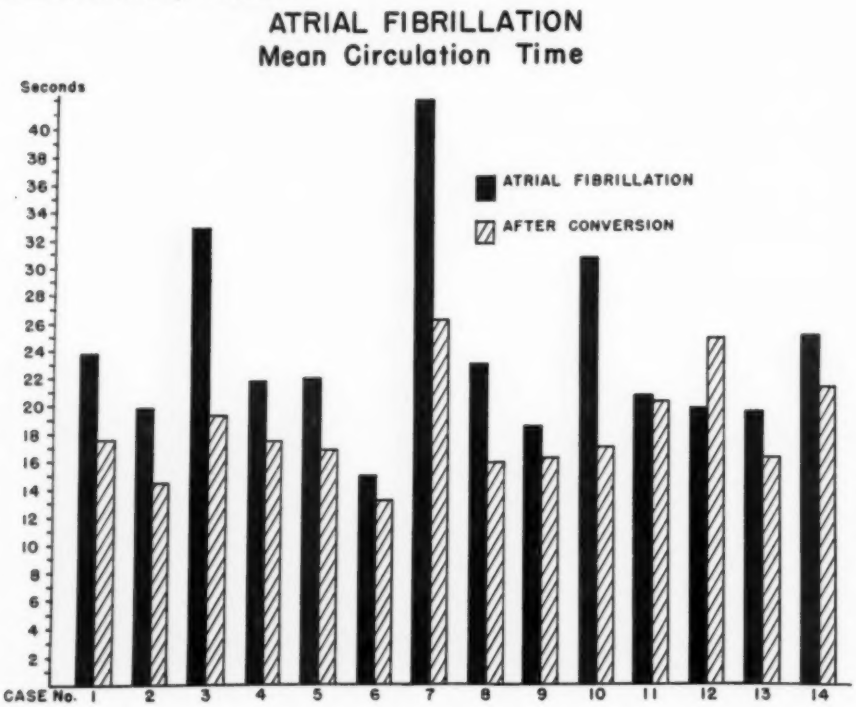

Fig. 8.

An over-all decrease in pulmonary blood volume was noted following conversion. In the seven patients in whom total blood volume was determined while fibrillating, the pulmonary blood volume averaged 28.2 per cent of the total. Following restoration of sinus rhythm the pulmonary blood volume in these seven patients averaged 23.4 per cent. This is above the value found by Ebert and associates[15] for normal patients, but well within the range found in patients with left ventricular failure. Since the dye was introduced into the pulmonary artery the lower value found in this group after conversion cannot be due to reduction in heart size. It can, therefore, be assumed that re-establishment of sinus rhythm reduces the so-called pulmonary blood volume. It cannot be definitely determined whether this is due only to the resumption of atrial systole,

or to an over-all improvement in cardiac function, but it is suggested that both factors are important.

Since most of the patients studied had, at some time during their illness, considerable elevation of systemic blood pressure, any persistent reduction in pressure would be likely to improve their cardiocirculatory function. It is interesting to note that eight patients had a significant fall in mean radial artery pressure following conversion with quinidine. It is justifiable to assume that restoration of a sinus rhythm per se would have little effect upon the radial artery pressure. In association with the fall in arterial pressure there was a concomitant fall in peripheral resistance in nine of the patients studied. This suggests a direct quinidine effect upon the peripheral vascular bed indicating a decrease in its resistance.

Although at the time of the initial study all patients with the exception of two had a venous pressure within the acceptable normal range and no patient manifested clinical evidence of decompensation, ten of the fourteen patients had a decrease in venous pressure following restoration of a sinus rhythm. Right atrial pressure was measured satisfactorily at both studies in only six patients, and in four of these a significant decrease in atrial pressure was observed. These changes in venous and atrial pressures imply that atrial systole has an important function in the cardiac cycle.

The contention that atrial systole plays only a minor role in cardiocirculatory function does not seem tenable in view of these results. After restoration of a sinus rhythm the increased rate of blood flow seems to be a constant finding. This cannot be ascribed to a change in ventricular rate as the average rate was 72 beats per minute while fibrillating and 66 per minute when regular. This change in the rate of blood flow appears to be the result of circulatory readjustments independent of ventricular rate and blood volume.

In an attempt to evaluate the changes noted after re-establishment of sinus rhythm in these patients, two factors should be kept in mind: the relative value of atrial systole in the cardiac cycle and the effect of quinidine upon the entire circulatory system. In our study, the average dose of quinidine was 1.4 Gm. daily. As shown by Ferrer and associates,[16] 0.8 Gm. of quinidine given orally in one dose to patients with severe cardiovascular disease was sufficient to lower the peripheral resistance and to increase the cardiac output in most of the patients studied.

It is evident that the restoration of sinus rhythm by quinidine has benefited this group of patients both subjectively and as manifested by the readjustment of the circulation. The importance of individual factors such as atrial systole and quinidine have not been separated and at the present time studies are continuing in an attempt to elucidate the role of the various factors involved including the relative effects of the quinidine itself, the optimum dose desired, and the change wrought by a resumption of atrial systole.

SUMMARY AND CONCLUSIONS

1. The hemodynamic effects of restoration of sinus rhythm by quinidine in fourteen patients with atrial fibrillation have been studied. These studies

have utilized the method of right heart catheterization using a modified dye injection technique.

2. Conversion to sinus rhythm by quinidine resulted in a significant rise in cardiac output and a decrease in pulmonary blood volume in the majority of patients studied.

3. The observed decrease in mean radial artery pressure and the decrease in peripheral resistance with a rise in cardiac output would suggest a peripheral arteriolar effect of quinidine.

4. The observed increase in rate of blood flow, the lower venous pressure, and the reduced right atrial pressure further demonstrate improvement in cardiovascular mechanics following resumption of a sinus rhythm.

5. The improvement in hemodynamic function observed in all patients during this study suggests that quinidine sulfate is of definite value in the treatment of patients with chronic auricular fibrillation.

REFERENCES

1. Wegria, Rene, Frank, C. W., Misrahy, G. A., Sioussat, R. S., Sommer, L. S., and McCormack, C. H., Jr.: Effect of Auricular Fibrillation on Cardiac Output, Coronary Blood Flow, and Mean Arterial Blood Pressure, Am. J. Physiol. **163**:135, 1950.
2. Goldman, M. J.: Quinidine Therapy of Auricular Fibrillation, Am. Heart J. **40**:93, 1950.
3. Askey, J. M.: Quinidine in the Treatment of Auricular Fibrillation in Association With Congestive Failure, Ann. Int. Med. **24**:371, 1946.
4. Kahn, C. M., and Levine, S. A.: An Evaluation of the Use of Quinidine Sulfate in Persistent Auricular Fibrillation, Ann. Int. Med. **8**:923, 1935.
5. Lyons, R. H., Kennedy, J. A., and Burwell, C. S.: Measurement of Venous Pressure by Direct Method, Am. Heart J. **16**:575, 1938.
6. Cournand, A., and Ranges, H. A.: Catheterization of the Right Auricle in Man, Proc. Soc. Exper. Biol. & Med. **46**:462, 1941.
7. Moore, J. W., Kinsman, J. M., Hamilton, W. F., and Spurling, R. G.: Studies on the Circulation. II. Cardiac Output Determinations; Comparison of the Injection Method With the Direct Fick Procedure, Am. J. Physiol. **89**:331, 1929.
8. Stewart, G. N.: The Pulmonary Circulation Time, the Quantity of Blood in the Lungs, and the Output of the Heart, Am. J. Physiol. **58**:20, 1921.
9. Aperia, A.: Hemodynamical Studies, Skandinav. Arch. f. Physiol, Supplement 16 (to 83), p. 1, 1940.
10. Hickman, J. B., and Cargill, W. H.: The Effect of Exercise on Cardiac Output and Pulmonary Arterial Pressure in Normal Persons and in Patients With Cardiovascular Disease and Pulmonary Emphysema, J. Clin. Investigation **27**:10, 1948.
11. Nicholson, J. W., III, and Wood, E. H.: Estimation of Cardiac Output and Evans Blue Space in Man, Using an Oximeter, J. Lab. & Clin. Med. **38**:588, 1951.
12. This laboratory. Unpublished data.
13. Cournand, A., Riley, R. L., Breed, E. S., Baldwin, E. deF., and Richards, D. W.: Measurement of Cardiac Output in Man Using the Technique of Catheterization of the Right Auricle or Ventricle, J. Clin. Investigation **24**:106, 1945.
14. Bolomey, A. A., Michie, A. J., Michie, C., Breed, E. S., Schreiner, G. E., and Lauson, H. D.: Simultaneous Measurement of Effective Renal Blood Flow and Cardiac Output in Resting Normal Subjects and Patients With Essential Hypertension, J. Clin. Investigation **28**:10, 1949.
15. Ebert, R. V., Borden, C. W., Wells, H. S., and Wilson, R. H.: Studies of the Pulmonary Circulation. I. The Circulation Time From the Pulmonary Artery to the Femoral Artery and the Quantity of Blood in the Lungs of Normal Individuals, J. Clin. Investigation **28**:1134, 1949.
16. Ferrer, M. I., Harvey, R. M., Werko, L., Dresdale, D. T., Cournand, A., and Richards, D. W., Jr.: Some Effects of Quinidine Sulfate on the Heart and Circulation of Man, Am. Heart J. **36**:816, 1948.

THE CIRCULATORY AND VENTILATORY CHANGES IN CHRONIC PULMONARY DISEASE AS AFFECTED BY LANATOSIDE C

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NEW HAVEN, CONN.

THE PURPOSE of this investigation has been to gather observations of the hemodynamics, ventilatory dynamics, and oxygen transport in various kinds of chronic pulmonary diseases before and after the administration of a digitalis preparation, lanatoside C. In addition to the standard ventilatory and circulatory studies, the present investigation is concerned with the intrapulmonary shunts which have been demonstrated in some cases of chronic pulmonary disease.[1,2] The use of lanatoside C serves two functions: creating an experimental situation by altering cardiopulmonary functions and their relation to one another; and providing some information of use in determining the therapeutic value of digitalis preparations in cardiopulmonary insufficiency.

Consideration of studies by other investigators shows that there are few consistent effects of digitalis unless one separates the patients into categories such as cases with high or low output failure, left or right ventricular failure, etc.[3-9] The scope of the present report does not include generalities about the action of digitalis in patients with pulmonary disease, but rather records specific observations of the effect of the drug on particular combinations of circulatory and ventilatory changes in individual patients.

METHODS

Nine patients from the University Medical Service of the Grace-New Haven Community Hospital were the subjects of this report. In each case either primary disease of the lung or deformity of the chest wall was found, and the patient had been referred to us for consideration of digitalis therapy. The clinical findings in each case are summarized in Table I. In all except two patients (Cases 3 and 9) a previous clinical trial of digitalis had been abandoned because the patient felt subjectively worse on the drug.

Cardiac catheterization was done while the patient was in a resting, fasting state. The period of study began at 8:30 A.M. and usually ended two or three hours later. No sedatives were used, but 1.5 Gm. of oral Pronestyl Hydrochloride was administered prior to the procedure in an effort to reduce the frequency of

From the Department of Internal Medicine and the Cardiovascular Study Unit, Yale University. This work was supported by a grant from the Life Insurance Medical Research Fund.

Received for publication March 10, 1952.

*Trainee of the National Heart Institute, United States Public Health Service, National Institutes of Health.

ventricular tachycardia which is often observed as the catheter tip passes through the right ventricle. Patency of the cardiac catheter was assured by maintaining a constant flow of sterile saline at a rate not exceeding 1 c.c. per minute.

After blood samples (for calculation of systemic blood flow) and pressure tracings were obtained, 1.6 mg. of lanatoside C was administered intravenously in one dose. In each case a digitalis effect was observed in the electrocardiographic tracing within fifteen to thirty-five minutes of giving the drug. Blood samples and pressure tracings were again obtained one hour after the injection of lanatoside C. Following this, oral digitoxin was administered in divided doses until a total dose of 1.2 mg. had been given by the next day.

Before and after digitalization, blood samples were obtained from the right ventricle (rather than from the pulmonary artery which might have been contaminated by systemic blood from bronchial to pulmonary artery communications) and from the femoral artery, and a sample of expired air was collected in a Douglas bag. Blood flow was estimated by applying the Fick principle to these data. Arterial blood samples were taken while the patient breathed room air and again after breathing pure oxygen for five minutes. Pressures were recorded by means of a multichannel Hathaway pressure unit with the table level as the zero point. Each patient's anteroposterior chest diameter in centimeters is included in Table IV so that hydrostatic pressure corrections can be made to any point.

The blood oxygen analyses were done by the Ordway modification of the method of Roughton and Scholander.[10] Analysis of this technique in our laboratory reveals a maximum difference between two independent analyses of single samples of ± 0.04 volumes per cent for arterial blood, and ± 0.08 volumes per cent for venous blood. The volume of the Douglas bag expired air sample was measured and the sample analyzed in the Scholander micro-gas analyzer.[11] Duplicate blood and respiratory gas analyses were done on each sample by different technicians. The oxygen consumed by the patient in one minute was calculated according to a standard method.[12]

Pulmonary function studies were done the day before and repeated the day after digitalization. They consisted of estimations of tidal volume, vital capacity, expiratory reserve volume, resting minute breathing volume, maximal breathing capacity, resting breathing reserve, and the ratio of breathing reserve to maximal breathing capacity.[13] A nine-liter recording bell-type respirometer was used for these studies. Functional residual capacity was estimated by a modification of the open method described by Darling, Cournand and Richards.[14]

Calculations.—Formulas for blood flow and shunts are those of Fick[15] and of Lundsgaard and Van Slyke[16] in which the symbols have been changed to conform to the standard terminology recommended by a group of physiologists in a joint editorial appearing in *The Federation Proceedings.*[17]

$$\dot{Q}b = \frac{\dot{V}o_2}{Ca_{o2} - C\bar{v}_{o2}}$$

$$\dot{Q}b_{EPF} = \frac{\dot{V}o_2}{C_LC_{o2} - C\bar{v}_{o2}}$$

$$\alpha = \frac{C_LC_{o2} - Ca_{o2}}{C_LC_{o2} - C\bar{v}_{o2}}$$

In addition a formula developed by Ordway[18] for calculating the amount of arterial oxygen unsaturation due to intrapulmonary factors which can be overcome by breathing pure oxygen was utilized:

$$L = \frac{(Ca_{o2o} - Ca_{o2}) - (Tb_{o2o} - Tb_{o2}) - (Cbd_{o2o} - Cbd_{o2})}{Tb_{o2}}$$

In all of the above, the symbols are used as follows:

$\dot{Q}b$ = Systemic blood flow in liters per minute.

$\dot{Q}b_{EPF}$ = Effective pulmonary blood flow in liters per minute as described by Bing and associates.[19]

$\dot{V}o_2$ = Total oxygen consumption in cubic centimeters per minute.

Ca_{o2} = Arterial blood oxygen content in volumes per cent × 10.

$C\bar{v}_{o2}$ = Mixed venous blood oxygen content in volumes per cent × 10.

α = Right-to-left shunt not overcome by breathing pure oxygen expressed as a per cent of the total systemic blood flow. This is a "net" value, being the algebraic sum of all right-to-left and left-to-right shunts.

C_LC_{o2} = Pulmonary capillary blood oxygen content in volumes per cent × 10. This value is derived from the expression: $(Tb_{o2} + Cbd_{o2} - L[Tb_{o2}])$

L = Per cent of hemoglobin passing through aerated pulmonary capillaries which, due to faulty ventilation or diffusion, is not fully oxygenated while breathing room air but becomes saturated while breathing pure oxygen.[16,20] The arterial saturation plus L cannot equal more than 100 per cent. That it may appear to do so is the result of using an arbitrary value for dissolved O_2.

Tb_{o2} = Total corrected blood oxygen capacity in volumes per cent × 10.

Cbd_{o2} = Oxygen physically dissolved in blood in volumes per cent × 10.

Subscript $_o$ after $_{o2}$ refers to functions estimated while breathing 100 per cent oxygen instead of room air.

The quantity of physically dissolved oxygen in arterial blood after breathing 100 per cent oxygen was not determined directly. It could be expected to lie somewhere between 1.0 volume per cent and 2.1 volumes per cent depending upon the effective tension of oxygen developed at the gas-blood barrier (Sendroy, Dillon, and Van Slyke[21]). In practice, by the methods used in the present study, it appears to lie between 0.6 and 1.4 volumes per cent. This range, together with an analysis of factors producing the low values, have been discussed by Preston and Ordway.[10] For this reason the value of 1.0 volume per cent for calculating L has been chosen arbitrarily.

TABLE I. CLINICAL OBSERVATIONS

CASE NO.	PATIENT	AGE (YRS.)	SEX	DURATION OF SYMPTOMS (YRS.)	DYSPNEA	CYANOSIS	CLUBBING	ANKLE EDEMA	RBC M/mm.^{3}	ECG	X-RAY	IMPROVED AFTER LANATOSIDE C
						Primary Diagnosis: Diffuse Pulmonary Granuloma (?Beryllosis)						
1.	D. B.	52	M	1	Marked	0	0	0	4.5	Normal (R.B.B.B.after lanatoside C)	Diffuse nodular infiltration	No
						Primary Diagnosis: Fibrosis and Emphysema						
2.	G. A.	55	M	10	Marked	0	0	0	5.1	Normal	Advanced emphysema	No
						Primary Diagnosis: Arrested Tuberculosis With Fibrosis						
3.	W. P.	40	M	16	Moderate	Minimal	0	0	5.3	Low T in L1, 2, CV_4, 6	Old tb., rt. lung. Left pneumonectomy and thoracoplasty	Yes
						Primary Diagnosis: Bronchiectasis						
4.	E. V.	40	M	15	Marked	Moderate	Moderate	Minimal	6.5	Moderate R.A.S.	Bronchiectasis, LLL, (lipiodal instillation)	Yes
5.	C. K.	57	M	2	Marked	Marked	Moderate	Moderate	5.6	Marked R.A.S.	Emphysema and fibrosis	Yes
6.	P. M.	41	M	12	Moderate	Minimal	Moderate	0	5.6	Normal	Bronchiectasis RLL, LUL; Emphysema	?
7.	C. S.	53	M	46	Moderate	Minimal	Moderate	0	5.9	Normal	Chronic pneumonitis RLL, lingula LUL; Emphysema	No
8.	D. H.	56	M	10	Minimal	Minimal	Minimal	0	4.9	Normal	Saccular bronchiectasis LUL, LLL, RUL	No
						Primary Diagnosis: Depressed Sternum						
9.	C. M.	28	F	7	Minimal	0	0	0	4.6	Normal	Pectus excavatum	?

Key:
R.B.B.B. = Right bundle branch block
R.A.S. = Right axis shift of the electrical axis
L.L.L. = Left lower lobe
R.L.L. = Right lower lobe
L.U.L. = Left upper lobe
R.U.L. = Right upper lobe

RESULTS

The clinical observations for each patient are summarized in Table I. Five of the cases had a major diagnosis of bronchiectasis, one of relatively pure emphysema, one of old pulmonary tuberculosis with fibrosis, emphysema, and previous right pneumonectomy, one of depression of the sternum, and one of diffuse pulmonary granulomatosis. This patient (Case 1) had a history of exposure to beryllium in that he had broken burned-out fluorescent bulbs in the course of his occupation as a trash collector. He had a typical beryllium granuloma of the skin with beryllium demonstrated in the biopsy specimen of this lesion. However, post-mortem analysis of the lung did not reveal a significant concentration of beryllium.*

The most constant complaint in this group of patients was dyspnea on exertion, occurring to some degree in each case. Cyanosis present in six of the nine cases was accompanied by polycythemia in five. Only Cases 4 and 5 showed right axis deviation of the electrocardiogram. Ankle edema was present in the same two patients, one of whom had an enlarged, tender liver. Both of these patients were relieved of their edema following digitalization. One patient (Case 1) who had not shown evidence of primary heart disease developed right bundle branch block after digitalization.

All patients received a full dose of 1.6 mg. of lanatoside C and developed S-T changes of the electrocardiogram associated with a digitalis effect. Following digitalization, three patients (Cases 3, 4, and 5) were subjectively improved in spite of the fact that one (Case 4) developed an alarming increase in cyanosis, and another (Case 3) developed minimal cyanosis. It was not possible, on clinical grounds, to say that the other patients were either improved or made worse.

The physiologic observations and calculated data for each patient before and after digitalization are listed in Tables II to V.

The oxygen consumption (Table II) varied in both directions, and probably reflects the difficulty of obtaining basal conditions in this type of patient. The blood-oxygen carrying capacities, however, remained quite constant in spite of the slow saline infusion. The respiratory quotient remained relatively constant.

In every case after digitalization (Table III) there was a rise in systemic blood flow although it may not have been significant in Cases 7 and 8. This rise was due to an increased stroke volume except in Cases 6 and 8 in which it was almost entirely the result of an accelerated heart rate, and in Case 3 where both rate and stroke volume increased. The diastolic filling time, which could be measured from pressure tracings taken before and after lanatoside C in five patients, was found to be shortened in two (Cases 1 and 8), lengthened in one (Case 3) and unchanged in two (Cases 2 and 9). The patients exhibiting the greatest increase in stroke volume (Cases 2 and 9) showed no change in diastolic filling time. In two patients (Cases 4 and 7), who also increased their stroke volume, the pressure tracings after digitalization were unsatisfactory for measuring the diastolic filling time.

*Analysis of the lung revealed less than 0.005 micrograms per 3.0 grams of wet lung tissue.

TABLE II. BLOOD AND RESPIRATORY GAS STUDIES BEFORE AND AFTER LANATOSIDE C

CASE NO.		O_2 USED C.C/MIN. ($\dot{V}_{o2}$)	R. Q.	BLOOD O_2 CONTENT, VOLUMES PER CENT					ARTERIAL BLOOD O_2 SATURATION (%)	$L \times 100$ (% of Tb_{o2})	$\alpha \times 100$ (% of $\dot{Q}b$)
				AMBIENT ARTERIAL (Ca_{o2})	AMBIENT VENOUS ($C\bar{v}_{o2}$)	ARTERIAL AFTER BREATHING O_2 (Ca_{o2o})	O_2 PHYSICALLY DISSOLVED (Cbd_{o2})	CORRECTED O_2 CAPACITY (Tb_{o2})			
1.	a.*	266	0.71	15.6	8.6	17.7	0.21	16.7	92	8	0
	b.	259	0.71	14.1	8.1	16.5	0.17	16.2	86	10	10
2.	a.	262	0.72	20.2	12.7	22.7	0.19	22.2	90	8	6
	b.	348	0.78	19.2	12.9	21.3	0.19	21.0	90	6	10
3.	a.	350	0.73	21.2	14.1	25.0	0.18	23.6	89	11	0
	b.	279	0.69	19.9	15.6	24.1	0.16	23.2	85	15	0
4.	a.	217	0.82	15.8	10.2	19.5	0.14	19.1	82	15	10
	b.	255	0.79	12.6	9.2	16.4	0.10	19.0	66	15	52
5.	a.	257	0.66	11.2	7.4	17.0	0.10	18.3	61	27	38
	b.	350	0.68	11.9	8.3	17.7	0.10	18.7	63	26	36
6.	a.	400	0.71	18.5	11.1	21.9	0.16	21.5	85	12	8
	b.	469	0.72	18.5	11.5	22.1	0.17	21.1	87	13	0
7.	a.	286	0.74	20.1	15.1	24.4	0.16	23.4	85	15	0
	b.	282	0.78	21.1	16.4	24.9	0.17	23.9	88	12	0
8.	a.	282	0.69	18.2	11.2	21.0	0.16	21.3	85	9	16
	b.	268	0.69	18.5	12.4	21.4	0.17	20.9	88	10	7
9.	a.	260	0.75	19.7	12.1	20.9	0.36	19.6	99	1	0
	b.	228	0.64	18.8	14.5	20.7	0.24	19.6	95	5	0

*a. = before lanatoside C; b. = after lanatoside C.

The mean atrial pressures (Table IV) in general followed the direction of change of the end-diastolic right ventricular pressure. Two of the patients (Cases 2 and 8) showed a significant rise in both mean atrial and right ventricular end-diastolic pressures, whereas two others (Cases 3 and 9) had a significant fall in right atrial pressure not associated in Case 9 with a similar fall in right ventricular end-diastolic pressure. The right ventricular and pulmonary artery systolic pressures rose after digitalization in each case in which satisfactory pressure tracings could be obtained. The brachial artery pressures varied slightly in either direction.

The arterial blood oxygen saturation which is inversely related to the L and α factors (Tables II, III) dropped significantly in two patients (Cases 1 and 4). In addition, α, L, or both were increased in five cases (Cases 1, 2, 3, 4, and 9).

TABLE III. CIRCULATORY DATA BEFORE AND AFTER LANATOSIDE C

CASE NO.		SYSTEMIC BLOOD FLOW, L./MIN. ($\dot{Q}b$)	EFFECTIVE PULMONARY BLOOD FLOW, L./MIN. ($\dot{Q}b_{EPF}$)	VENTRICULAR DIASTOLIC FILLING TIME (SEC./BEAT)	STROKE VOLUME (C.C./BEAT)	RATE PER MINUTE
1	a.*	3.80	3.80	0.58	45	84
	b.	4.32	3.86	0.55	51	84
2.	a.	3.49	3.28	0.44	40	88
	b.	5.53	4.97	0.44	67	82
3.	a.	4.93	4.93	0.37	52	94
	b.	6.49	6.49	0.41	63	103
4.	a.	3.88	3.50	0.28	34	115
	b.	7.50	3.64	—	65	115
5.	a.	6.77	4.22	—	—	—
	b.	9.73	6.25	—	—	—
6.	a.	5.41	5.00	0.45	67	81
	b.	6.70	6.70	—	67	100
7.	a.	5.72	5.72	—	69	83
	b.	6.00	6.00	—	80	75
8.	a.	4.03	3.40	0.45	40	100
	b.	4.39	4.05	0.41	41	107
9.	a.	3.42	3.42	0.45	46	75
	b.	5.30	5.30	0.45	71	75

*a. = before lanatoside C; b. = after lanatoside C.

The effective pulmonary blood flow which has been defined as ". . . the volume of blood which, after its return to the right auricle, ultimately reaches the pulmonary alveoli . . ."[19] does not include blood shunted past nonaerated alveoli unless it is returned to aerated alveoli via collateral channels. As would be expected, it increased with the systemic flow, but the increment varied inversely with the α and L factors.

*a. = before lanatoside C; b. = after lanatoside C.

TABLE IV. BLOOD PRESSURE DATA BEFORE AND AFTER LANATOSIDE C

CASE NO.		ANTERIOR-POSTERIOR THICKNESS OF PATIENT'S CHEST (Cm.)	PRESSURE IN mm. Hg AT TABLE LEVEL				
			RIGHT ATRIUM (MEAN)	RIGHT VENTRICLE	PULMONARY ARTERY	PULMONARY CAPILLARY	BRACHIAL ARTERY
1.	a.*	20	3	33/5	27/13	—	104/56
	b.		5	43/2	40/17	3	110/60
2.	a.	24	6	23/6	—	5	112/80
	b.		12	34/12	—	16	118/84
3.	a.	25	22–34‡	61/22	61/40	37	118/86
	b.		15	64/16	67/40	—	124/86
4.	a.	24	20	28/15	—	—	130/90
	b.		22	—	—	—	120/84
5.	a.	†	1	51/0	51/20	—	110/80
	b.		1	90/1	—	—	110/76
6.	a.	†	5	32/4	—	—	130/85
	b.		–5	—	—	—	140/98
7.	a.	†	14	—	—	—	144/82
	b.		14	—	—	—	140/92
8.	a.	25	4	27/0	27/14	—	180/115
	b.		15	50/16	—	—	180/110
9.	a.	19	22	23/10	20/14	14	124/74
	b.		7	32/11	—	9	126/70

*a. = before lanatoside C; b. = after lanatoside C.
†Patient in sitting position, pressures corrected to a level 5 cm. below sternal angle.
‡Marked respiratory variation.

A decreased vital capacity (Table V) was present in all patients except the one (Case 9) with a depressed sternum. In each case in which it was estimated the predigitalization functional residual capacity was above normal (normal value is 1.8 to 2.5 liters in this laboratory) except in Case 3 in which one lung had been removed. Four patients showed a significant rise (over 100 c.c.) and one (Case 6) a significant fall following digitalization. The base line maximal breathing capacity was depressed far below normal in every patient (normal being over 100 liters/minute). Following digitalization it rose significantly in six individuals (Cases 1, 2, 4, 6, 7, and 9), remained constant in two (Cases 3 and 8), and dropped in one (Case 5). The ratio of breathing reserve to maximal breathing capacity (normal above 0.90) rose significantly in two patients (Cases 1 and 2) but otherwise varied little.

TABLE V. PULMONARY FUNCTION STUDIES BEFORE AND AFTER LANATOSIDE C

TABLE V. PULMONARY FUNCTION STUDIES BEFORE AND AFTER LANATOSIDE C

CASE NO.		VOLUME IN LITERS				LITERS PER MINUTE			RATIO Br.R/M.B.C.
		TIDAL VOLUME	VITAL CAPACITY	FUNCTIONAL RESIDUAL CAPACITY	EXPIRATORY RESERVE VOLUME	MINUTE BREATHING VOLUME	MAXIMAL BREATHING CAPACITY	BREATHING RESERVE	
1.	a.*	0.539	1.481	—	0.819	16.7	49.2	32.5	0.66
	b.	0.477	1.430	—	0.777	16.9	60.9	44.0	0.72
2.	a.	0.760	2.436	6.7	0.881	10.6	25.9	15.3	0.59
	b.	0.622	2.436	6.6	0.788	8.8	29.8	21.0	0.70
3.	a.	0.716	1.369	1.51	0.332	10.9	56.9	46.0	0.81
	b.	0.705	1.451	1.88	0.321	10.0	57.0	47.0	0.83
4.	a.	0.622	1.350	—	0.310	8.0	41.0	33.0	0.81
	b.	0.658	1.541	—	0.400	10.0	56.0	46.0	0.82
5.	a.	0.623	1.600	—	—	12.1	25.9	13.8	0.53
	b.	0.550	1.638	—	—	10.5	22.0	11.5	0.52
6.	a.	0.518	1.700	4.65	0.540	15.1	53.7	38.6	0.72
	b.	0.623	1.754	3.77	0.540	14.2	61.0	46.8	0.77
7.	a.	0.498	1.845	5.08	0.674	8.9	38.9	30.0	0.77
	b.	0.612	2.198	6.64	1.016	9.3	42.7	33.4	0.78
8.	a.	0.560	1.710	5.24	0.446	11.2	20.7	9.5	0.46
	b.	0.529	1.680	5.38	0.404	10.3	19.4	9.1	0.47
9.	a.	0.518	3.431	3.65	1.265	9.1	36.3	27.2	0.75
	b.	0.757	3.576	4.80	1.203	11.4	41.4	30.0	0.72

*a. = before lanatoside C; b. = after lanatoside C.

DISCUSSION

Each of the patients studied showed a rise in systemic blood flow after digitalization. Since most studies have shown a drop in systemic blood flow following digitalis in normal individuals,[9,22] the findings here would suggest that these patients had abnormal hearts even though several did not have all the criteria for a diagnosis of cor pulmonale.

Since none of the subjects of this report had auricular fibrillation, and only two had frank signs of congestive heart failure, it is impossible to state definitely that digitalization was achieved in every case. However, a large dose of lanatoside C was used, and an electrocardiographic effect of the drug was obtained in each case, hence there is a reasonable certainty that the changes observed represent a digitalis glycoside action.

In most cases, the work of the heart was increased after digitalization as manifested by increased stroke volume, increased developed tension, or both. (In Case 6 it cannot be said that the work was increased since postdigitalization ventricular or pulmonary artery pressures could not be obtained.) From the data presented here it cannot be determined whether the increased work was a function of increased energy release, that is, myocardial oxygen consumption, or of increased mechanical efficiency. Recent work of Bing and associates[23] would suggest the latter, although, at least in the patients exhibiting evidence of congestive failure, the studies of Starling and Visscher[24] would favor an increased oxygen consumption as well.

The increased stroke volume observed in six cases could not be correlated with changes in diastolic filling time or heart rate. It is not likely that the greater stroke volume represented greater initial fiber length (at least in Case 4 which had evidence of congestive failure) since Bing and associates have shown that, under these circumstances, the fiber length decreases on digitalization.[23] A more likely explanation is that the residual volume decreased, that is, a greater proportion of the diastolic volume was ejected with systole.

The rise in mean atrial and end-diastolic right ventricular pressures seen in two patients is not in accord with the observations of other investigators.[3,4,6,7] The apparent discrepancy in atrial pressure observations may in part have been related to the increased intrapleural pressure excursions found in diseases associated with bronchial obstruction or decreased pulmonary elasticity. It is conceivable, however, that the shortening of the myocardial fiber induced by digitalis,[23] if proportionately greater than the increase in stroke volume, could be associated with an increase in initial tension. Observations of right atrial pressures in cases of mitral stenosis before and after digitalization have suggested that an early rise, corresponding to that seen in the present cases, may be followed by a drop to a level below the predigitalization level after a longer period of time.[25]

The increase in right ventricular and pulmonary artery systolic pressures observed in some of the patients studied is consistent with the findings of other investigators[7] and is related to an increase in the work of the heart. Insufficient data were observed to allow speculations concerning changes in pulmonary vascular resistance.

Of considerable interest was the drop in arterial blood oxygen saturation observed in several of the patients. When formulas are applied which separate "inaccessible" or "shunting" factors (α) from the "ventilatory and diffusion" factor (L), it may be seen that either or both can be responsible for increased anoxemia after digitalization. The inexact nature of these calculations becomes obvious when one considers the assumptions necessary for their use.[2] However, they probably give a rough idea of circulatory pathways, and since the inaccuracies are probably constant before and after digitalization, the relative changes would be significant.

The adverse effect of a lowered arterial oxygen saturation is, probably, most keenly felt by the central nervous tissue.[26] In addition, our experience with coronary artery catheterization has indicated a coronary arteriovenous oxygen difference of about 12 volumes per cent.[27] Clearly, unless coronary blood flow increases considerably, adequate oxygen cannot be supplied to the myocardium when the arterial content falls to almost 12 volumes per cent as in Case 4, and this at a time when the cardiac output had almost doubled!

The inefficiency of increased systemic blood flow after digitalization in some cases of chronic pulmonary disease is demonstrated by the extremely small rise in effective pulmonary blood flow associated with a considerably greater rise in systemic blood flow seen in Cases 4 and 5. On the other hand, Case 6 showed an increase in efficiency of blood flow in terms of oxygenation or effective flow.

The one patient (Case 9) who had a fivefold increase in L factor also had a great increase in functional residual capacity. An increased functional residual capacity in the absence of marked hyperventilation might produce an increase in the L factor. It is conceivable that the increased blood flow at a higher mean pressure produced engorgement of the pulmonary vessels with a decreased elasticity of the lung leading to ventilation at an overdistended level. This was partly, but not completely, compensated for by an increase in minute ventilation. The two patients showing the more pronounced drop in arterial oxygen saturation did so by virtue of an increase in the α factor. A number of possible explanations can be offered for this phenomenon. Some evidence has been advanced in favor of direct arteriovenous shunts between the pulmonary arteries and veins,[28] and the increase in pulmonary artery pressure occurring after lanatoside C might increase the blood flowing through these shunts. Others have described an increased blood flow through bronchial veins in chronic pulmonary disease.[29,30] Liebow has suggested that, in some of these cases, there might be a reversal of flow from the azygous vein to the pulmonary vein through these channels.[30] It is hard to see, however, how digitalis preparations could increase the volume of the reverse flow through these channels, although they must be borne in mind as additional shunts. As another mechanism, it is possible that, in the predigitalization state, a maximum flow of blood is already perfusing the "accessible" or ventilated pulmonary capillaries, and with a greater blood flow after digitalization, the increase is shunted through inaccessible or nonventilated pulmonary capillaries, thereby increasing the proportion of nonaerated blood mixing with aerated blood in the pulmonary veins. Finally, the presence of collateral blood flow between systemic and pulmonary arteries has been demonstrated in cases of

chronic lung disease.[1,29,31] This left-to-right shunt tends to reduce the anoxemic effect of pulmonary artery to vein shunts.[2] It is conceivable that the increase in pulmonary artery pressure subsequent to digitalization decreases this collateral flow by decreasing the pressure differential between the systemic and pulmonary arteries, thereby causing a rise in the α factor.

The deleterious effect of a greater L factor associated with an increase in functional residual capacity after digitalization has already been commented on in regard to Case 9. In addition, many patients complained of dyspnea and subjective respiratory discomfort after digitalization. This might well be the effect of increased lung distention reflected by the increase in functional residual capacity. The apparent improvement in ventilatory dynamics suggested by an increase in maximal breathing capacity after digitalization in six cases may be the effect of better cardiac function. The rise, in two cases, of both the maximal breathing capacity and functional residual capacity seems inconsistent, but the changes are not great.

The only factors in the clinical observations common to all patients in this group were the two which constituted the criteria for selection of patients, namely, the presence of some form of pulmonary disease or chest deformity, and the question, raised by an attending physician, of the advisability of digitalization. It is not surprising, therefore, that the physiologic findings appear heterogeneous. In recapitulation, however, it becomes apparent that there is a pattern of response to lanatoside C common to all of the patients in this study. The cardiac output invariably increased, and the stroke volume likewise increased in most cases. The ventricular systolic pressure rose in the six cases in which measurements could be made after digitalization, hence it can reasonably be assumed that the work of the heart increased.

These consistent hemodynamic changes would appear to reflect the direct effect of lanatoside C on the ventricular myocardium. The response of the ventilatory tests on the other hand were variable, suggesting that lanatoside C had no direct effect on these functions, but only influenced them by virtue of its hemodynamic effect.

In the complex and varied pulmonary diseases represented by the group of patients studied, the effect of the altered hemodynamic pattern on ventilation and lung volumes appears to be unpredictable.

Before the present study was begun, three cases of sudden death occurring shortly after digitalization had been observed in this hospital in patients with chronic pulmonary disease. The question of whether these deaths were part of the natural course of the disease or were related to digitalization cannot be answered from the data in this report, but some of the possible immediate deleterious effects of digitalization have become evident. In the present group of patients these effects were a rise in right atrial mean and right ventricular end-diastolic pressures (two patients); an increase in functional residual capacity (four patients); and greater right-to-left intrapulmonary shunting of blood as indicated by lowered arterial blood oxygen saturation and higher L and α factors (four patients).

These deleterious effects did not occur consistently in all patients, and, indeed, one patient who obtained clinical benefit from digitalization appeared to suffer the greatest increase in right-to-left shunt. It seems likely, therefore, that the immediate beneficial and deleterious effects of digitalis in a case of cardiopulmonary disease can go hand in hand. Later physiologic readjustments[7,25] may partially overcome the deleterious effect. Thus one should be concerned about supporting the patient during the "dangerous" period beginning with the onset of the digitalis effect and lasting until central venous pressure, functional residual capacity, and arterial oxygen saturation have returned toward predigitalization levels. In addition, factors such as pulmonary infection contributing to a lowered arterial oxygen saturation should be treated, whenever possible, before digitalization is attempted in a patient with chronic pulmonary disease.

SUMMARY

1. Circulatory and ventilatory studies before and one hour after the administration of 1.6 mg. of lanatoside C to nine patients with chronic pulmonary disease are reported.

2. Clinical improvement occurred in only three cases.

3. The most consistent effect of the digitalis glycoside was an increase in the work of the heart as manifested by a rise in systemic blood flow and ventricular systolic pressure.

4. Deleterious effects occurring in some cases were an increase in right atrial mean and right ventricular end-diastolic pressures, an increase in functional residual capacity, and a decrease in arterial blood oxygen saturation.

5. The causes of these effects and their relation to therapy are discussed.

The authors are indebted to Mrs. Betty Ackerman, Miss Evelyn Haller, and Miss Dorothy Nixon for their assistance in performing the technical procedures involved in this study.

REFERENCES

1. Liebow, A. A., Hales, M. R., and Lindskog, G. E.: Enlargement of the Bronchial Arteries and Their Anastomoses With the Pulmonary Arteries in Bronchiectasis, Am. J. Path. **25**:211, 1949.
2. Gray, F. D., Jr., Lurie, P. R., and Whittemore, R.: Circulatory Changes in Chronic Pulmonary Disease. A Study of Pulmonary Collateral Circulation, Yale J. Biol. & Med. **23**:380, 1951.
3. McMichael, J., and Sharpey-Schafer, E. P.: The Action of Intravenous Digoxin in Man, Quart. J. Med. **13**:123, 1944.
4. Stead, E. A., Jr., Warren, J. V., and Brannon, E. S.: Effect of Lanatoside C on the Circulation of Patients With Congestive Failure, Arch. Int. Med. **81**:282, 1948.
5. Wood, P., and Paulett, J.: The Effect of Digitalis on the Venous Pressure, Brit. Heart J. **11**:83, 1949.
6. Lagerlöf, H., and Werkö, L.: Studies on the Circulation in Man. V. The Effect of Cedilanid (Lanatoside C) on Cardiac Output and Blood Pressure in the Pulmonary Circulation in Patients With Compensated and Decompensated Heart Disease, Acta Medica Belgica, Tome **4**: Fasc. I, 1, 1949.
7. Ferrer, M. I., Harvey, R. M., Cathcart, R. T., Webster, C. A., Richards, D. W., Jr., and Cournand, A.: Some Effects of Digoxin Upon the Heart and Circulation in Man, Circulation **1**:161, 1950.
8. Bayliss, R. J. S., Etheridge, M. J., Hyman, A. L., Kelly, H. G., McMichael, J., and Reid, E. A. S.: The Effect of Digoxin on the Right Ventricular Pressure in Hypertensive and Ischaemic Heart Failure, Brit. Heart J. **12**:317, 1950.

9. Harvey, R. M., Ferrer, M. I., Cathcart, R. T., and Alexander, J. K.: Some Effects of Digoxin on the Heart and Circulation in Man. Digoxin in Enlarged Hearts Not in Clinical Congestive Failure, Circulation **4**:366, 1951.
10. Preston, S. N., and Ordway, N. K.: Observations of Arterial Oxygen Content in Children During the Inhalation of Air and 100% Oxygen, Am. J. Physiol. **152**:696, 1948.
11. Scholander, P. F.: Analyzer for Accurate Estimation of Respiratory Gases in One-half Cubic Centimeter Samples, J. Biol. Chem. **167**:235, 1947.
12. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, ed. 3, Baltimore, 1943, Williams & Wilkins Company.
13. Baldwin, E., de F., Cournand, A., and Richards, D. W., Jr.: Pulmonary Insufficiency. I. Physiological Classification, Clinical Methods of Analysis, Standard Values in Normal Subjects, Medicine **27**:243, 1948.
14. Darling, R. C., Cournand, A., and Richards, D. W., Jr.: Studies on the Intrapulmonary Mixture of Gases. III. An Open Circuit Method for Measuring Residual Air, J. Clin. Investigation **19**:609, 1940.
15. Fick, A.: Ueber die Messung des Blutquantums in den Herzventrikeln, Sitz. Phys. Med. Ges. Würzburg, p. 16, 1870.
16. Lundsgaard, C., and Van Slyke, D. D.: Cyanosis, Medicine **2**:1, 1923.
17. Editorial: Federation Proc. **9**:602, 1950.
18. Ordway, N. K.: Formulas for the Calculation of Right-to-left, Left-to-right and Mixed Shunts in Congenital Heart Disease. To be published.
19. Bing, R. J., Vandam, L. D., and Gray, F. D., Jr.: Physiological Studies in Congenital Heart Disease. I. Procedures, Bull. Johns Hopkins Hosp. **80**:107, 1947.
20. Berggren, S. M.: The Oxygen Deficit of Arterial Blood Caused by Nonventilating Parts of the Lung, Acta physiol. Scandinav. **4**: Supp. XI, 1942.
21. Sendroy, J., Jr., Dillon, R. T., and Van Slyke, D. D.: Studies of Gas and Electrolyte Equilibria in Blood. XII. The Solubility and Physical State of Uncombined Oxygen in Blood, J. Biol. Chem. **105**:597, 1934.
22. Bing, R. J., Maraist, F. M., Dammann, J. F., Jr., Draper, A., Jr., Heimbecker, R., Daly, R., Gerard, R., and Calozel, P.: Effect of Strophanthus on Coronary Blood Flow and Cardiac Oxygen Consumption of Normal and Failing Human Hearts, Circulation **2**:513, 1950.
23. Bing, R. J., Falholt, W., Heimbecker, R., and Carroll, D.: Myocardial Oxidative Metabolism and Initial Fiber Length of the Failing Human Heart, J. Clin. Investigation **30**:630, 1951.
24. Starling, E. H., and Visscher, M. B.: The Regulation of the Energy Output of the Heart, J. Physiol. **62**:243, 1927.
25. Gray, F. D., Jr., and Gray, F. G.: The Circulatory and Ventilatory Changes in Mitral Stenosis as Affected by Lanatoside C. To be published.
26. Comroe, J. H., Jr., and Dripps, R. D.: The Physiological Basis for Oxygen Therapy, Springfield, Ill., 1950, Charles C Thomas, Publisher.
27. Gray, F. D., Jr., and Gray, F. G.: Unpublished data.
28. Tobin, C. E., and Zariquiey, M. O.: Arteriovenous Shunts in the Human Lung, Proc. Soc. Exper. Biol. & Med. **75**:827, 1950.
29. Marchand, P., Gilroy, J. C., and Wilson, V. H.: An Anatomical Study of the Bronchial Vascular System and Its Variations in Disease, Thorax **5**:207, 1950.
30. Liebow, A. A.: Personal communications.
31. Cockett, F. B., and Vass, C. C. N.: A Comparison of the Role of the Bronchial Arteries in Bronchiectasis and in Experimental Ligation of the Pulmonary Artery, Thorax **6**:268, 1951.

ESOPHAGEAL PRESSURE PULSE PATTERNS (ESOPHAGEAL PIEZOCARDIOGRAM).

I. Experimental Observations*

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THIS IS a report of an investigation into the relationship between the pulsations which can be observed and recorded in the esophagus at the level of the left atrium, and their progenitors, the pressure pulse patterns of the left atrium itself.

In order to avoid repetition of the cumbersome title of esophageal pressure pulse pattern and to distinguish these tracings clearly from esophageal electrocardiography, the term "esophageal piezocardiogram" is suggested. The term indicates simply that the recordings are made via the esophagus, that they are recordings of pressure (piezo) and that their origin lies in the cardiac (left atrial) pressure pulsation.

In 1880 Rosenthal,[1] and in 1883 Kronecker and Melzer,[2] reported that during esophagoscopy they had observed pulsation which was synchronous with the heart beat in localized areas of the esophageal wall. One of these areas of pulsation was that portion of the anterior wall of the esophagus which was adjacent to the posterior wall of the left atrium. The pulsations at this level were first recorded and studied in dogs by Fredericq[3] in 1887 and it was he who suggested that a relationship existed between these esophageal pulsations and the pressure pulses of the left atrium.[4] The first recordings in human beings were obtained in 1889 by Sarolea[5], who was a pupil of Fredericq.

In the years immediately following the demonstration that graphic recordings could be made, a number of investigators tried to apply the technique to the diagnosis of mitral valve disease and the study of atrial arrhythmias.[6-10] This earlier work did not succeed in conclusively establishing the origin and form of the pulse waves in various pathologic states, nor was a relationship to events occurring within the left atrium definitely established. Consequently, findings were conflicting. Studies made later by Taquini[11] and by Groedel[12] and by Puddu and Sibilia,[13] with somewhat more adequate recording apparatus did tend to show that a characteristic pattern could be observed in mitral insufficiency in human beings. However, even this work was not completely convincing because the curves which they obtained showed comparatively minor alterations from those found in normal individuals. Moreover, the patterns did not resemble

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Received for publication May 12, 1952.

*Aided by a grant from the Udo M. Reinach Fund.

either the left atrial pressure or volume curves obtained by Wiggers and Feil[14] in dogs with acute mitral insufficiency.

In spite of the conflicting and inconclusive findings of these scattered investigations it was decided to restudy the problem because of the potential clinical usefulness of a technique which might afford an insight into the pressure pulses of the left atrium. The problem was approached by setting up a relatively standard recording apparatus and technique and then, in dogs, simultaneously recording the pulse waves within the esophagus and the pressure pulses directly from within the left atrium.[15] Such recordings were made following the production of mitral insufficiency and stenosis, congestive failure, and during the administration of pressor substances. The tracings which were obtained differed considerably from those of previous investigators. The explanation may be found in a consideration of the differences in technique.

All earlier recording had been done with latex balloons attached to a rubber gastric tube. This tube was then passed into the esophagus, the balloon was positioned at the level of the left atrium, and inflated to a variable degree with air. The pressure-sensitive element was a rubber tambour. Such elastic, air-filled systems allow for substantial volume displacement, and therefore record volume changes but do not accurately portray pressure variation. They cannot be readily standardized or calibrated. To render the apparatus more sensitive to pressure change, the volume displacement permitted in the system was greatly reduced by employing (1) a water-filled balloon and completely water-filled system, (2) Polythene tubing, and (3) a relatively rigid pressure sensitive element, that is, Sanborn electromanometer.

It was also observed that as the balloon was distended with successive volumes of fluid, a point was reached beyond which equal increments of volume resulted in decreasing increments of pressure within the system. Therefore, when recordings of the pulse pressure within the esophagus were made, the balloon was distended to only that degree at which a constant pressure-volume relationship was maintained. At first latex condoms were used. Later it was found that heavier rubber such as that in rubber gloves gave a more desirable pressure-volume relationship.

This is certainly in no sense a rigid, isometric system since both the balloon, the heart, and the esophagus itself are moveable and distensible. However, it is more so than the previously-used elastic air systems and, as will be seen, the tracings obtained are surprisingly similar to pressure tracings obtained simultaneously within the left atrium.

METHOD

The esophageal tube consisted of a length of Polythene tubing whose inner diameter was 3.5 mm. One end was sealed and two openings into the lumen were cut in the sides of the tube about 3 cm. from the sealed end. A rubber sleeve was secured to the tube so as to cover both openings. The inside of the rubber balloon was in communication, therefore, with the lumen of the Polythene tubing through these openings. A three-way stopcock, attached to the open end of the

tube, served to connect it with both a saline-filled syringe and the lead tubing leading to the pressure transducer. All pressures were recorded with Sanborn electromanometers and a four-channel Sanborn direct writing electrocardiograph. Paper speed was 50 cm. per second so that each small vertical division represented 0.02 second.

Since both the esophageal and atrial pressures were transmitted approximately equal distances through fluid-filled rigid tubing under similar conditions of pressure, it was felt that no differences in timing existed.

Adult dogs were anesthetized with Nembutal. Endotracheal and esophageal tubes were inserted. The esophageal balloon was distended with saline as previously described. This resulted in a static pressure within the system of between 9 and 17 mm. Hg. Tracings were then taken at various levels within the esophagus. From previous experience it was usually possible to identify an atrial pattern which will be described later. The esophageal tube was then fixed at this level. Intermittent positive pressure respiration was begun and the chest was opened. The balloon position was then verified by direct palpation, and repeat tracings were taken. A left superior pulmonary vein was ligated distally and a No. 8F cardiac catheter inserted through it into the left atrium. Simultaneous atrial and esophageal pressure curves and Lead II of the electrocardiogram were then recorded. The pericardium was opened sufficiently to expose the left atrial appendage but not enough to dislocate the heart. Further tracings were obtained. In one group of animals, the left atrial appendage was amputated and mitral insufficiency was produced by cutting either the medial or lateral cusp with a blunt-end scissors. A distinct thrill was always palpable. Several of these animals were given intravenous injections of 0.2 c.c. to 0.5 c.c. of a 1 per cent solution of Neosynephrine to demonstrate the effects of acute elevation of blood pressure upon the magnitude of regurgitation. At the conclusion, the dogs were sacrificed and the hearts examined to verify the degree and location of the lesions.

An attempt was made, in a second group of animals, to simulate the cardiodynamics of mitral stenosis by passing a ligature around the left ventricle and through the interventricular septum just below the annulus fibrosis. The method was not satisfactory for protracted experiments, because coronary circulation was constricted, but it did suffice for the recording of acute changes. Congestive failure was observed in another experiment following a protracted tachycardia induced by Adrenalin infusion.

RESULTS

The curves obtained in eighteen normal animals and in ten following the production of mitral insufficiency are sufficiently similar so that a detailed description of representative samples will illustrate the main features of this entire group.

In Fig. 1, the tracings show: (1) esophageal pulsation in the normal animal with closed chest, (2) the same animal after the pericardium has been opened, and (3) same animal following the production of mitral insufficiency. The first

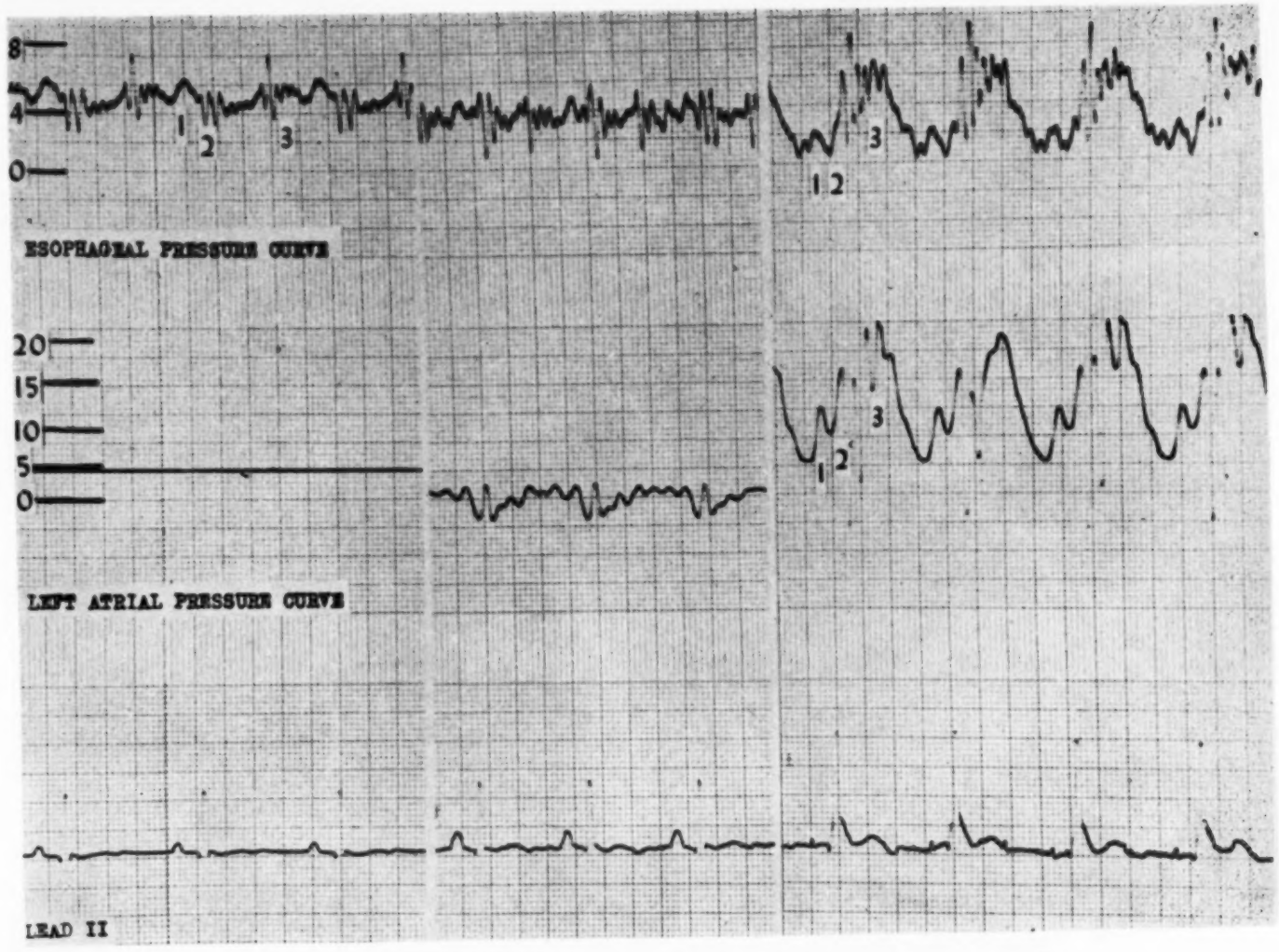

Fig. 1.—*A*, The normal esophageal pressure curve: *1*, atrial systole; *2*, onset of ventricular systole, and, *3*, reopening of the mitral valve. *B*, Simultaneous left atrial pressure curve and esophageal pressure curve in normal animal with open chest and pericardium. *C*, Tracings following the production of mitral insufficiency which exhibit a positive pressure wave during ventricular systole (between *2* and *3*).

pulse wave tracing (*A*) is typical of that observed in the intact animal. It is characterized by a positive presystolic wave (*1*) which follows the onset of the P wave of the electrocardiogram by 0.04 to 0.06 second. It is similar in contour and timing to the wave of atrial systole observed in the atrium itself. This is followed by a series of rapid oscillations (*2*) which occurs during the first heart sound and probably represents its low-frequency components. During ventricular systole, the pressure either falls somewhat as in this illustration or remains at the level reached at the end of atrial systole. The curve then rises in a gentle slope and a second set of rapid oscillations (*3*) is superimposed upon its summit. These are found to occur during the second heart sound and to precede the fall in pressure which marks the reopening of the mitral valve.

The tracings seen in Fig. 1,*B*, show that the opening of the pericardium has not modified the pulse contour appreciably and the same general features are noticed as in Fig. 1,*A*. The pressure curve obtained directly from the atrium (middle tracing) needs no comment. The only noticeable feature is the pronounced wave of mitral closure. This has been observed similarly by Wiggers and Feil[14] in dogs.

The tracings seen in Fig. 1,*C*, following the cutting of the valve, give unmistakable evidence of mitral insufficiency both in the esophageal (top) and the atrial (middle) pressure tracings. In both, a positive wave of atrial systole (*1*) is easily identified. The beginning of ventricular contraction is signalled by a sharp rise of pressure (*2*) beginning 0.04 second after the Q wave of the electrocardiogram. The atrial pressure curve displays several marked pressure oscillations during the early phase of ventricular ejection, then a sustained midsystolic rise reaching a peak just prior to reopening of the mitral valve. Finally, a rapid fall in pressure at (*3*) marks the opening of the mitral valve. The approximate mean atrial pressure has risen from 0 mm. Hg to about 12 mm. Hg. The pulse tracings obtained synchronously in the esophagus display, with minor differences, the same features as the atrial curve itself. Evidence of the regurgitation jet early in the course of ventricular ejection is shown by the early, beginning elevation of the curve. The continuous midsystolic pressure rise, the late systolic peak followed by the precipitous descent of the curve are features which are seen to parallel the atrial pressure curve very closely.

There was no attempt made to maintain a constant basal pressure line or zero line in esophageal tracings, and these tracings were arbitrarily centered. The chief interest lay in the determination of the form of the pulse wave and in the calculation of the pulse pressure. By pulse pressure is meant the difference in pressure between the peak which occurs just before the mitral valve opening and the pressure recorded just prior to the onset of ventricular systole. A difference of 14.5 mm. Hg is recorded in the atrium and 5.5 mm. Hg in the esophagus.

In order to demonstrate that the elevated pressure seen during ventricular systole in the esophageal tracings was not somehow due to an arterial impact, the aorta was compressed at its root. Fig. 2 shows the tracings obtained in another animal just prior to compression of the aorta (*A*), during compression (*B*), and as the aorta was released (*C*). The compression of the aorta resulted in an increase in the maximum atrial pressure from 16.6 mm. Hg to 110 mm. Hg.

FIG. 1.—*A*, The normal esophageal pressure curve: *1*, atrial systole; *2*, onset of ventricular systole, and, *3*, reopening of the mitral valve. *B*, simultaneous left atrial pressure curve and esophageal pressure curve in normal animal with open chest and pericardium. *C*, Tracings obtained [illegible]

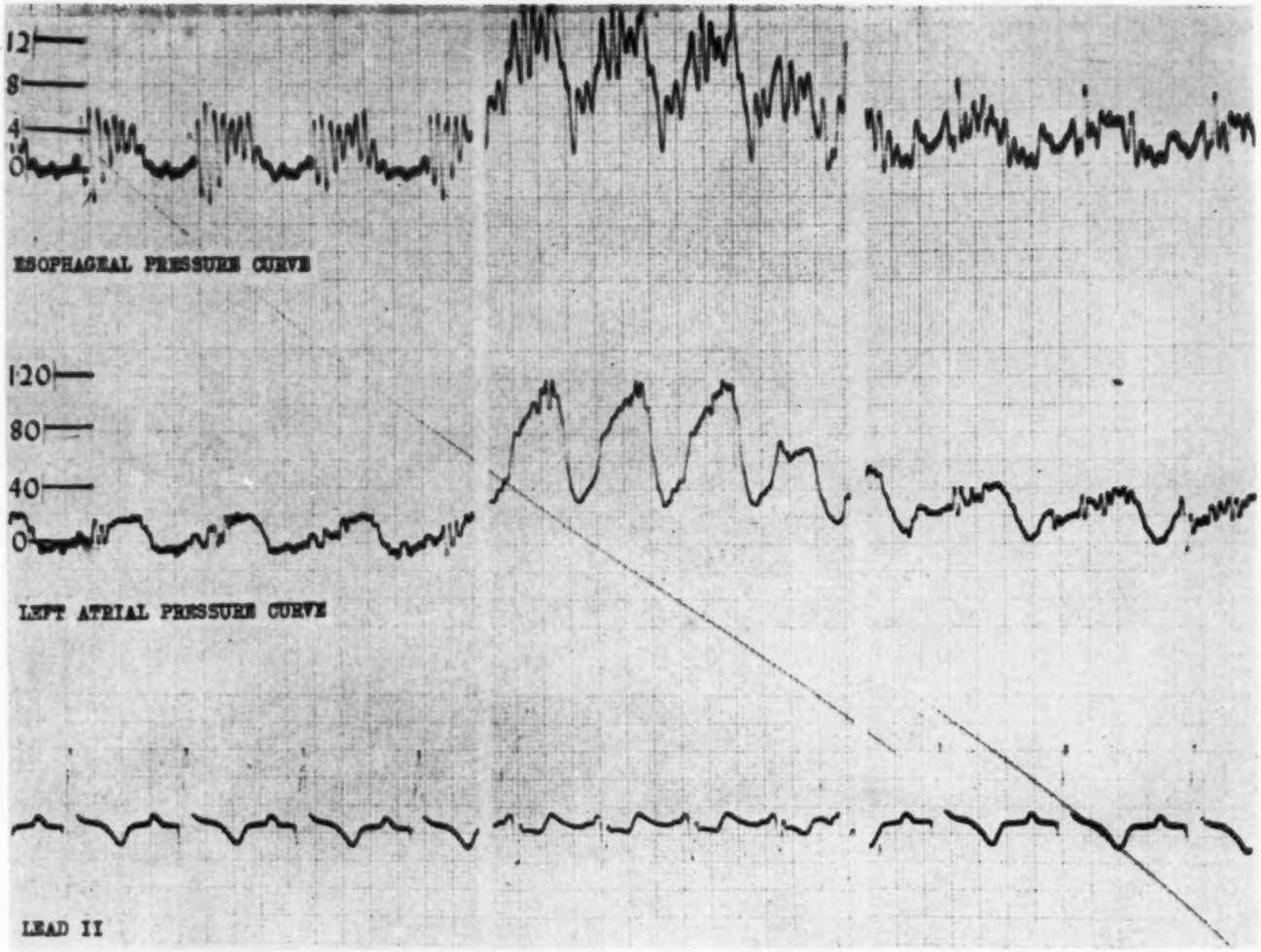

Fig. 2.—The effect of compression of the root of the aorta in the presence of mitral insufficiency. *A*, Following the production of mitral insufficiency. *B*, Following compression of the root of the aorta. Note the parallel rise in pressure in both the left atrial and esophageal pressure curves. *C*, Following release of compression. Note the parallel fall in pressure in the atrial and esophageal curves.

This is an increase of more than 600 per cent. The pressure in the atrium just prior to ventricular systole increased from −3 mm. Hg to 40 mm. Hg. The pulse pressure in the atrium during ventricular systole, therefore, increased from 19.6 mm. Hg to 70.0 mm. Hg. This phenomenon of an increased regurgitation volume following increase of peripheral resistance was originally shown by Wiggers and Feil.[14]

The pulse tracings from the esophagus clearly show an elevation of the maximum pressure (6 to 15.5 mm. Hg), elevation of the end-diastolic filling pressure (0.6 to 6 mm. Hg), and increased pulse pressure (5.4 to 9.5 mm. Hg).

Figs. 3 and 4 demonstrate the effects produced by the administration of Neosynephrine in the presence of mitral insufficiency. Fig. 3 illustrates the accentuation of regurgitation following intravenous injection of 2 mg. of Neosynephrine. The first set of tracings (*A*) were obtained after the chest had been opened and before valvular damage had been created. The characteristics of both the esophageal tracing (top) and the atrial tracing (middle) need no comment. They display the same features as were originally described (Fig. 2,*A*). The tracings of Fig. 3,*B*, were made after creation of a mitral lesion. The esophageal tracing (top) shows: (1) a barely discernible wave of atrial systole, (2) an elevation of pressure during the early and middle phases of ventricular systole with a gradually rising slope reaching a peak just before mitral valve reopening, and (3) a rapid fall following the opening of the mitral valve. The atrial tracings (middle) show these same characteristics. The next set of tracings (*C*) were made following the intravenous injection of 2 mg. of Neosynephrine. This has resulted, first, in an intensification of the pressure wave during atrial systole. Second, without any increase in the anatomic lesion, the pressure elevation in the atrium during ventricular systole has been greatly accentuated, and the angle of inclination of this pressure rise is much greater than before. Finally, the pressure maximum, which is reached after the termination of ventricular systole, is much higher. The "pulse pressure" has increased from 3.7 mm. Hg to 7.5 mm. Hg in the esophagus and from 15 mm. Hg to 27.2 mm. Hg in the atrium. The ratio of atrial to esophageal pulse pressures, however, has remained practically constant being 4.0 to 1 in Fig. 3,*B*, and 3.6 to 1 in Fig. 3,*C*.

Fig. 4 is a continuous recording made following the intravenous injection of 2 mg. of Neosynephrine into an animal in whom a substantial insufficiency had been produced. As the drug action increases in intensity one can observe the development of an accentuated atrial systolic pulse wave, the gradual increase in angle of inclination of the pressure rise during ventricular systole, and an increasing pressure maximum. The illustration is included because it again shows the remarkably close parallel between the tracings obtained from the esophagus and those of the left atrium.

It would seem, from these tracings, that the contour of the pressure pulse curve of the left atrium is very closely approximated by the curves of the transmitted pulsations recorded in the esophagus. Mitral valvular insufficiency is therefore readily discernible by the presence of characteristic positive pressure

mitral insufficiency. *B*, Following compression of the root of the aorta. Note the parallel rise in pressure in both the left atrial and esophageal pressure curves. *C*, Following release of compression. Note the parallel fall in pressure in the atrial and esophageal curves.

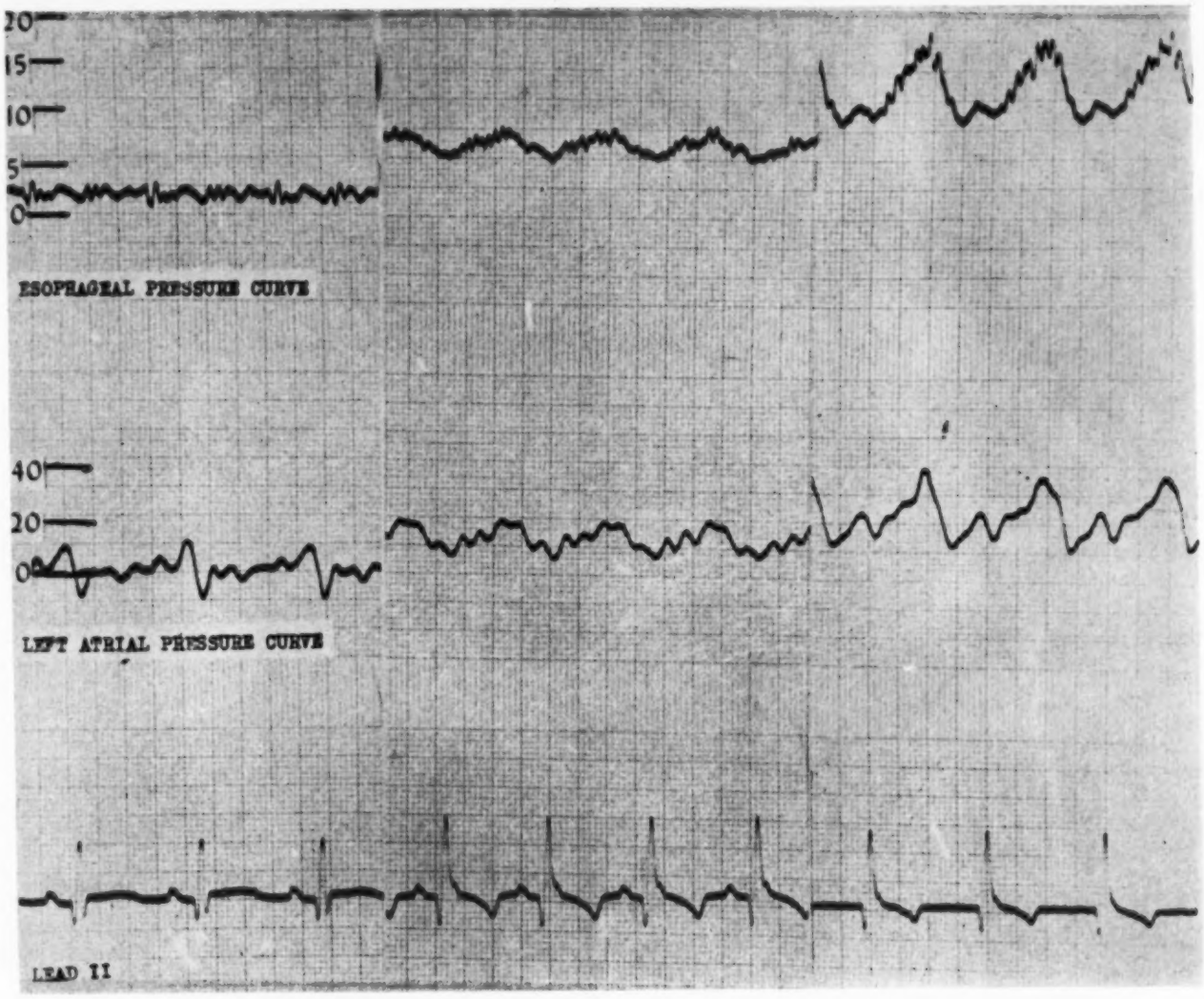

Fig. 3.—The effect of a pressor substance (Neosynephrine Hydrochloride) on the magnitude of regurgitation. *A*, Normal. *B*, Following production of mitral insufficiency. Note presence of a small positive pressure wave during ventricular systole. *C*, Following injections of 2 mg. of Neosynephrine Hydrochloride. Note the great increase in the magnitude of the positive pressure wave during ventricular systole in both the atrial and esophageal curves.

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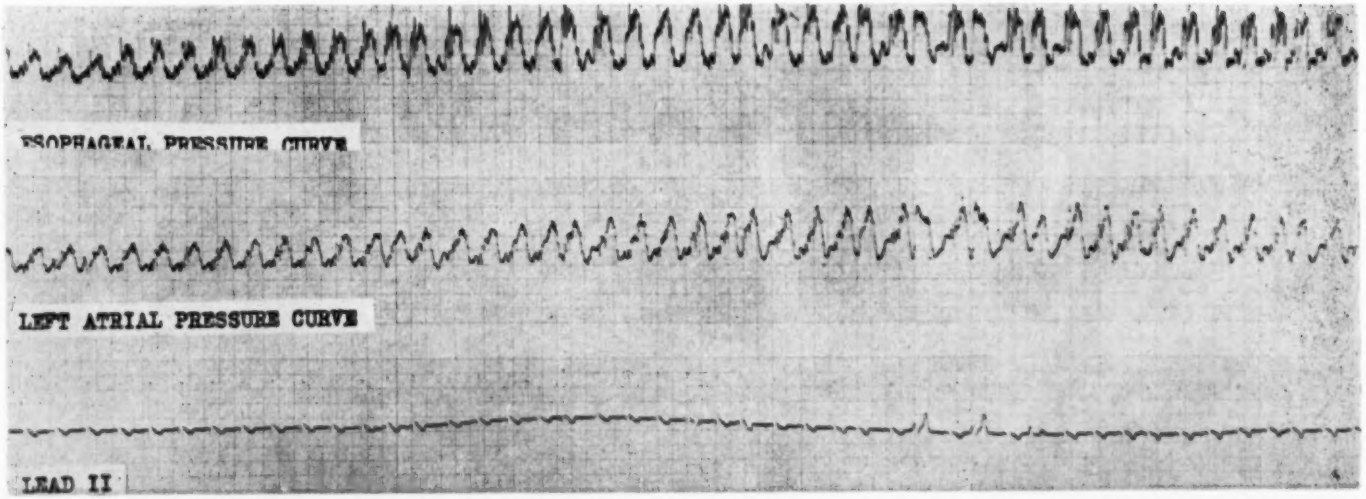


Fig. 4.—Following injection of a pressor substance (Neosynephrine Hydrochloride, 2 mg.) after the production of mitral insufficiency. Note the great similarity between the contours of each of the individual esophageal and the corresponding left atrial pressure curves.

wave during the period of ventricular systole. The curve of this pressure wave begins its ascent in early systole, rises progressively during the period of ventricular ejection, and reaches a peak just prior to the reopening of the mitral valve at the end of systole. Gorlin and associates[16] have reported very similar curves obtained in human beings with mitral insufficiency by the technique of "pulmonary capillary pressure" recording.

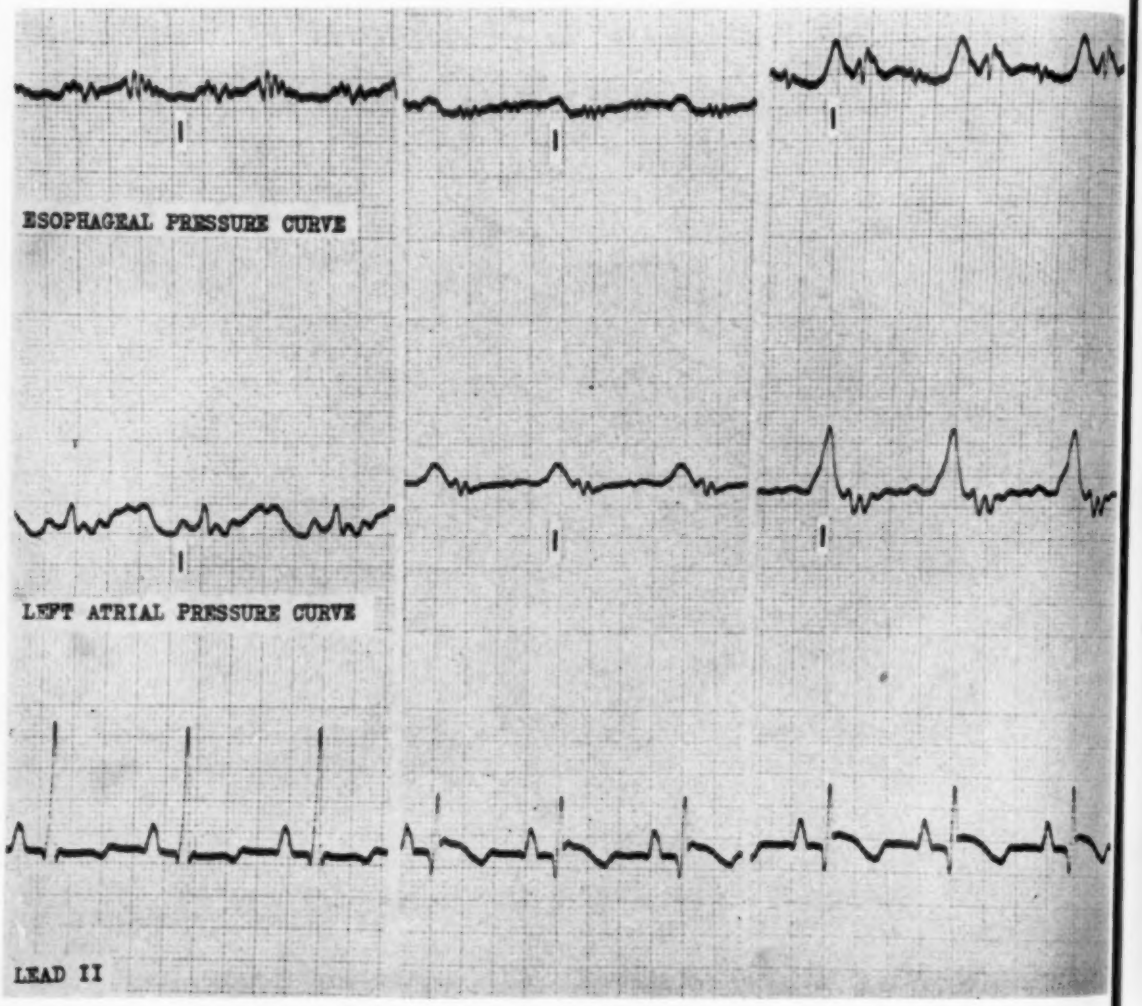
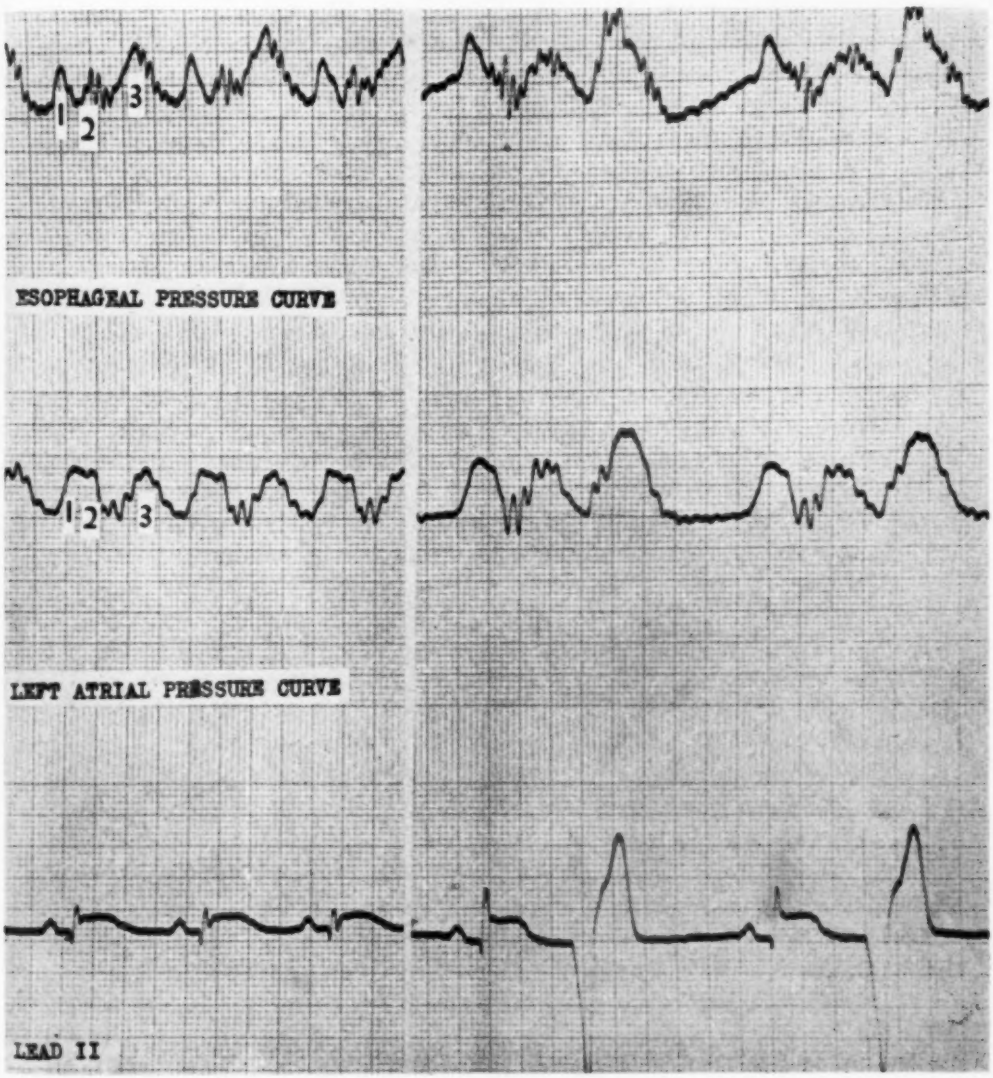


Fig. 5.—The relationship between the amplitude of the pressure during atrial systole in the left atrial and esophageal pressure curves. *A*, Normal. There is a barely perceptible pressure peak of atrial systole. *B*, Slight increase in the amplitude of the atrial systolic pressure peak in both the esophageal and atrial curves. *C*, Marked increase in amplitude of the atrial systolic pressure peak in both curves.

The tracings in Fig. 5 demonstrate the interesting fact that an increase in the magnitude of the pressure during atrial systole which results, presumably,

from an increase in the vigor of atrial contraction is reflected in esophageal recordings. The tracings were obtained successively as a ligature around the mitral annulus was gradually tightened. Fig. 5,*A*, represents the normal pattern. Atrial contraction produces a small pressure rise in the atrial pressure tracing (middle) and a barely distinguishable positive wave in the esophageal tracing (top). Fig. 5,*B*, shows an increased amplitude of atrial systole in both records. Fig. 5,*C*, shows a very pronounced atrial systolic peak which is faithfully transmitted to the esophageal recording system.



A. *B.*

Fig. 6.—Tracing of left ventricular failure. *A*, Note increased amplitude of pressure during atrial systole (*1*) and the presence of an accentuated "v" wave (*3*). *B*, Note the presence of bigeminal rhythm and similarity between the left atrial and esophageal pressure curves.

The final tracings, Fig. 6, are representative of another type of auricular pressure pattern. These were obtained from an animal in heart failure whose heart became considerably dilated following a protracted supraventricular tachycardia induced by a large dose of Adrenalin. The noteworthy feature is the presence of a late systolic pressure rise which is analagous to the accentuated "v" wave seen in the right atrial and venous pulse tracings of patients with right-sided heart failure. There is also an increase in the magnitude of the pressure during atrial systole.

DISCUSSION

It is apparent from these tracings that all phases of pressure fluctuation within the left atrium are demonstrable in the recordings from the esophagus. A particularly surprising finding has been the fact that the pressure curve which results from atrial systole itself is so faithfully transmitted in contour and magnitude. The pressure elevation within the atrium during atrial systole is due to active contraction and presumably should result in a decrease in the dimensions of that chamber. If all parts of the atrium actually contract concentrically, reducing the size of the chamber, then one would anticipate a negative wave in the esophagus during this period of the cardiac cycle. Actually, considerable controversy existed among previous investigators on this very point, some reporting negative waves[3,5] and others [6,7] variably positive ones.[8,10] This present study appears to us to have resolved all doubts about the presence of a positive pressure wave in the esophagus during atrial systole.

The presence of such a positive wave indicates that, during atrial systole, pressure is being exerted against the recording balloon. Moreover, the pressure exerted varies with the magnitude of the pressure attained during the contraction. There is no ready explanation for this observed fact. It is possible that the muscular contraction results in a change in the shape of the atrium so that the shortening of its horizontal and vertical dimensions results in an increase in the anteroposterior diameter resulting in a backward bulging. It is also conceivable that segments of the posterior wall of the atrium are actually forced outward by the increased pressure of systole. It is known that excitation does not occur simultaneously in all muscle groups of the atrial wall. There is, rather, a progressive entry into contraction of the various fractionate groups.[17] Finally, it is possible that this component of the curve is contributed by the pulmonary veins. We have no data to indicate the true explanation.

It is not difficult to see why the pressure variations during the remainder of the cardiac cycle are in phase in both the esophagus and the atrium. With the exception of atrial systole, the atrium is a passive muscular sac in which an increased pressure is the reflection of an increased volume. The increasing volume of the chamber imposes a pressure on all surrounding structures, and the balloon in the esophagus is compressed between the expanding atrium and the rigid vertebral column. The compression of the balloon results in an increase in pressure within the recording system and a positive wave is thus registered whenever the pressure within the atrium rises. Therefore, the entire contour of the left atrial pressure pulse curve is closely approximated by the esophageal pressure tracing.

Though this relationship between the *contour* of the two curves is apparent, the relationship between the *magnitudes* of pressure fluctuation in the respective curves is very difficult to formulate in general terms because many factors which cannot be quantitated influence the recording system. First, the actual pressure within the atrium at any instant depends upon the relationship between the mean tensile strength of the atrial wall and the atrial volume at that instant. This relationship in vivo is a complex one as is the case with all such elastomeric substances.[18] Second, the pressure developed within the recording system is the resultant of two forces. One force is imposed by the expanding atrium which compresses the balloon against the vertebral column. The other force is the expression of the resistance of the balloon and esophagus to the change in shape imposed by the first force. It is apparent, then, that the pressure within the recording system within the esophagus at any instant is the resultant of several variables even under the rather standard conditions of the experimental situation. It would also be anticipated that variations in the position of the heart in the chest, level of the diaphragm during respiration, proximity of the esophagus to the atrium, presence of hypertrophy of the atrial wall or of mediastinal disease might further alter a quantitative relationship in an unpredictable fashion.

It might be pointed out that, in the experimental preparations wherein these above factors were standardized, there was a rough correlation between the magnitude of the pressure fluctuation within the atrium and the esophagus. The average ratio between the two pressure values in the ten animals with varying degrees of mitral insufficiency was 3.3 to 1 with a range of 2.3 to 4.0 to 1.

CONCLUSION

A study was made in dogs of the pulsations which could be recorded in the esophagus at the level of the left atrium and a technique for such recording was described. Simultaneous recordings of these esophageal pulsations and the pressure pulses within the left atrium in a variety of experimental situations demonstrated that the two pulse wave contours were essentially identical.

It was therefore concluded that a good qualitative replica of the left atrial pressure pulse curve could be obtained by this technique. Constant normal patterns were found. A characteristic pulse wave contour was observed following the production of acute mitral regurgitation. Pressor substances were observed to augment the magnitude of this regurgitation.

It is proposed that these recordings be called esophageal piezocardiograms.

We wish to express our appreciation to Mr. Paul Geller and Mrs. Selma Rachlin for their technical assistance.

REFERENCES

1. Rosenthal, I.: Neue Studien ueber Atembewegungen, Arch. f. Anat. u. Physiol. suppl. Bd. 1880:24-40.
2. Kronecker, H., and Melzer: Der Schluckmechanismus, Arch. f. Anat. u. Physiol. suppl. Bd. 1883:338-362.
3. Fredericq, L.: Trav. Labor Liege II **127:** 1887-1888.
4. Fredericq, L.: Zentralbl f. Physiol. **22:**297, 1908.

5. Sarolea: La pulsation cardio-esophagienne chez l'homme, Buol. de l'acad. roy. de belge **18**:772, 1889.
6. Rautenberg, E.: Deutsches Arch. f. klin. Med. **91**:251, 1907.
7. Young, C. I., and Hewlett, A. W.: The Normal Pulsation Within the Esophagus, J. M. Research **11**:427, 1907.
8. Lian, C.: Les methodes de laboratoire dans le diagnostic de l'insufficiance mitrale, Arch. d. mal. du coeur **7**:385, 1909.
9. Janowski, W.: Das Oesophagokardiogram, Seine Erklarung und Bedeutung, Ztschr. f. klin. Med. **70**:211, 1910.
10. Clerc, A., and Esmein, C.: Etude critique de la' pulsation oesophagienne chez l'homme, Arch. d. mal du coeur **3**:1, 1910.
11. Taquini, A. C.: Exploration del Corazon per Vie Esophagica, Buenos Aires, 1936, El Ateneo.
12. Groedel, F. M.: The Venous Pulse and Its Graphic Recording, New York, 1946, Brooklyn Medical Press.
13. Puddu, V., and Sibilia, D.: Soffio Sistolico e Insufficienza Mitralica, Cuore e circolaz. **26**:2, 1942.
14. Wiggers, C. J., and Feil, H.: Heart **9**:119, 1922.
15. Lasser, R. P., and Loewe, L.: Characteristic Pressure Pulses Recorded With an Esophageal Balloon in Experimental Mitral Insufficiency in Dogs, Proc. Soc. Exper. Biol. & Med. **77**:798, 1951.
16. Gorlin, R., Lewis, B. M., Haynes, F. W., and Dexter, L.: Studies of the Circulatory Dynamics at Rest in Mitral Valvular Regurgitation With and Without Stenosis, Am. Heart J. **43**:357, 1952.
17. Wiggers, C. J.: Circulation in Health and Disease, Philadelphia, 1923, Lea & Febiger.
18. King, A. L., and Lawton, R. W.: Elasticity of Body Tissues, Medical Physics, Vol. II. Chicago, 1950, The Year Book Publishers, Inc.

THE LOW FREQUENCY TRACINGS OF THE PRECORDIUM AND EPIGASTRIUM IN NORMAL SUBJECTS AND CARDIAC PATIENTS

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THE FIRST low frequency tracings were obtained by Marey and Potain who recorded the motion of the heart by applying a capsule over the cardiac apex.[1] For many decades, the typical apical tracing (or apical cardiogram, or cardiogram) was considered that presenting a positive, plateaulike wave during systole.

Another recording apparatus was a box containing a spring ending with a button, to be pushed against an intercostal space; this box was connected with a Marey's capsule by means of a rubber tube. In a second technical stage, a Frank's capsule recorded on photographic film the vibrations of the membrane of a Marey's tambour applied over the apex (Cushney,[2] Hess,[3] Weitz,[4] and Weber[5]). It was soon recognized that the cardiograms have different aspects in the sitting, the supine, and the left-sided position.[5,6]

Apex cardiograms were recorded by Lewis,[7] Wolferth and Margolies,[8] Battro and associates[9] in cases of bundle branch block, and by Viciu[10] in congenital heart disease.

In a third technical stage, a crystal microphone with a "linear" type of response was used by Miller and White[11] and by Rappaport and Sprague.[12] The pulsations of the precordium set up changes of pressure in a small funnel; the stresses transmitted by the air to the crystal of Rochelle salt of the microphone are transformed into equivalent electrical pulsations and are recorded by an ordinary electrocardiograph.

Epigastric tracings were recorded early by students of cardiology. Mackenzie[13] first described this tracing. Lang[14] and Dressler[15] analyzed its waves. A detailed study was made by Fukui[16] in 1928. Interest of the tracing consisted mainly in the possibility of recording movements of the right heart through the diaphragm. However, pulsations of the left ventricle, the liver, and the abdominal aorta have to be reckoned with. Again, three technical stages took place: first, a Marey's capsule with tracings recorded on smoked drums; then, a Frank's capsule with mechanical-photographic recording; later on, use of the crystal microphone and electrical records.[17]

From the Laboratory of Cardiology of The Chicago Medical School and The Mount Sinai Hospital. This study has been aided by a grant of the Chicago Heart Association.

Received for publication May 30, 1952.

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Systematic studies were made by one of us[17] of the low-frequency tracings of the precordium and the epigastrium both in normal subjects and in cardiac patients.

A low frequency tracing of the chest can be recorded also by using an electromanometer, as demonstrated by Johnston and Overy.[18] The chest piece is connected by a short piece of hard rubber tubing to the lead tube of the electromanometer; the latter is provided with a high sensitivity microphone and the whole system is filled with air.

TECHNIQUE

Our study was partly made on the collection of tracings from the files of the Laboratory of Cardiology and partly on new records of patients of Mount Sinai Hospital. As a preliminary step, a comparative study was made in normal subjects between linear cardiography and manometric cardiography. Comparison was made by applying over various points of the chest a funnel connected by a T tube to both a linear microphone and a high sensitivity electromanometer. The tracings were recorded by means of a Sanborn Poly-Viso with direct writing—one channel transcribing the linear tracing, the other, the manometric tracing.

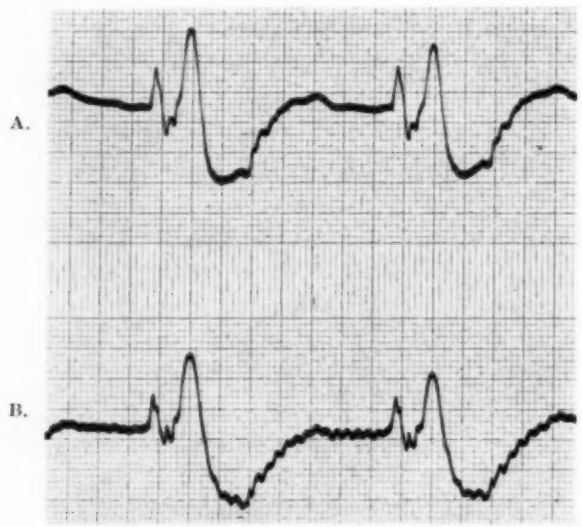

Fig. 1.—Comparison of a low frequency tracing recorded by a "linear" microphone (*A*) and an electromanometer (*B*).

As shown in Fig. 1, there are small differences between the tracings. The more rapid vibrations, corresponding to the rapid phases of the tracing, are slightly larger in the linear tracing. The manometric tracing presents smaller waves in correspondence with the heart sounds and possibly a more exact tracing during the slow phases of filling of the chambers. These minor differences did not seem to indicate a basic difference in the faithful reproduction of the tracing. Linear cardiography is simpler from a technical point of view and is based on portable instrumentation: therefore, it was considered not only that the tracings of our

collection were reliable but also that new tracings to be recorded in the daily study of cardiac patients should be recorded with the same procedure.

The usual technique of recording is the following: The patient is placed in a supine or semirecumbent position with complete muscular relaxation. A rubber strap is placed around the chest. A low funnel of 5 cm. in diameter with a side opening is screwed onto a "stethoscopic" microphone and placed over any point of the precordium, or at the epigastrium, and held in place by the rubber strap. Thus two simultaneous tracings can be recorded: one is a tracing of the high-frequency vibrations of the chest or epigastrium, corresponding to a stethoscopic phonocardiogram; the other is a low-frequency tracing of the chest or epigastrium. On the other hand, if one wishes to record a low frequency tracing of one area of the chest or abdomen and a phonocardiogram of another area, two funnels are used. One is connected with the linear microphone and placed on one point of the precordium while another funnel is connected with a stethoscopic microphone and placed over that area presenting the most distinctive acoustic phenomena (heart sounds or murmurs). The funnel records pulsations from about two intercostal spaces in the adult.

The following areas of the precordium were investigated: apex, midprecordium, pulmonic area, aortic area, and tricuspid area. In several cases, the suprasternal notch and the epigastrium were also studied.

A Sanborn Stetho-Cardiette was used as recording apparatus. One channel was used for sound tracings while the other recorded the low frequency tracing.

CLINICAL MATERIAL

All cases in which low-frequency tracings had been recorded were reviewed. The tracings were but one part of the complete study of the patient. Therefore, correlations were made in each case with the electrocardiogram, the phonocardiogram, the orthodiagram, and the clinical study. In some of the patients, ballistocardiograms, electrokymograms, and arterial and venous tracings were also recorded.

A total of 250 cases were studied. These were classified as shown in Table I.

The low frequency tracing of the apex was recorded in all cases; the epigastric tracing was recorded in 105 cases, and the various regional cardiograms were recorded in 108 cases.

RESULTS AND DISCUSSION

Normal Precordial Tracings.—The low frequency tracing (cardiogram) is the resultant of several factors:

1. *Movements* of the heart, and especially of the apex, together with better contact of the ventricular wall due to rotation of the apex and stiffening of the ventricular mass during the tension period.
2. *Changes in volume* of the heart due to decrease of the ventricular mass during ejection and its increase during diastole.
3. *Pulsations* of the large arteries, more or less directly transmitted.

The movements of the heart are particularly well recorded over the apex when the subject is either lying on his left side or sitting. The volume changes are

TABLE I

Normal subjects	28
Rheumatic heart disease	85
Mitral valve lesions only	56
Insufficiency	20
Stenosis	12
Both	24
Mitral and tricuspid lesions	4
Mitral and aortic lesions	13
Mitral, aortic, and tricuspid lesions	12
Congenital heart disease alone, or congenital and rheumatic lesions	16
Syphilitic heart disease	12
Calcific aortic stenosis or atherosclerotic aortic insufficiency	5
Cor pulmonale	3
Hypertensive heart disease	31
Coronary heart disease	49
Atrioventricular block	4
Adhesive or constrictive pericarditis (in 11 cases, only stringlike adhesions)	17
Total	250

recorded better over the midprecordium in the supine position. The arterial pulsations are recorded best at the base.

A small upright and rounded wave can be observed in the cardiogram during presystole. This is related to atrial contraction and is caused by rapid inflow of blood entering the ventricles, as proved by cases of complete heart block. The curve starts to rise at the beginning of ventricular systole; the onset of motion occurs between the Q and R waves of the electrocardiogram and with the first slow wave of the phonocardiogram in cases of auricular fibrillation. This rise, due to hardening of the ventricular mass during the tension period, reaches a peak which is simultaneous with that part of the first sound which marks the closure of the atrioventricular valves. Following a notch, the curve frequently rises again at the beginning of ejection, simultaneously with the opening of the semilunar valves.

Two main types may be seen. In the first, a systolic plateau constitutes the main part of the tracing. This indicates predominance of motion phenomena in the tracing (Figs. 2 and 5,*A*). In the second, a deep, inverted wave occurs during systole, changes of volume having predominance over evidence of motion (Figs. 3 and 5,*B*). In most tracings, the curve rises again after the systolic depression, reaching a peak at the time of closure of the semilunar valves. From this point on, the different cardiograms are similar, whatever direction the waves had during systole.

Since diastole is accompanied by two phases of more rapid inflow, there are two main diastolic waves in the cardiogram. The first is the wave of rapid filling during early diastole. This is usually well defined and its peak is simultaneous with the third heart sound. A deep depression is present between the notch which accompanies the main vibration of the second sound and that simultaneous with the third. Its lowest point occurs at the time of, or slightly before, the v wave of the jugular and hepatic tracings (opening of the atrioventricular valves).

The second phase of rapid filling, caused by atrial contraction, takes place soon before the following contraction and may seem part of the impulse due to ventricular contraction.

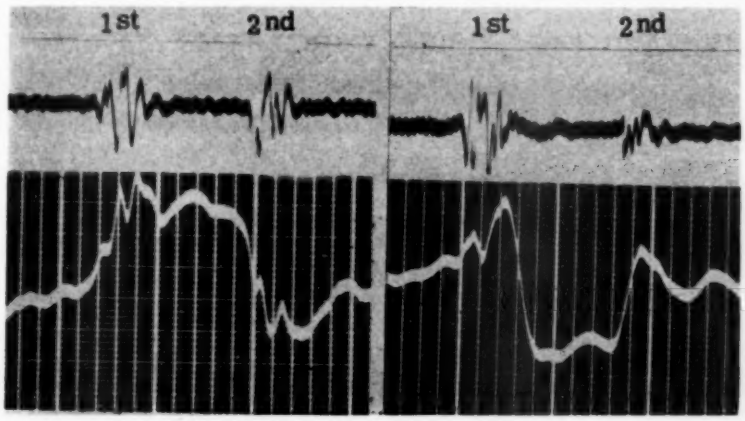

Fig. 2. Fig. 3.

Fig. 2.—Low frequency tracing at the apex. Normal subject (17 years of age). Plateaulike systolic wave (predominance of motion).

Fig. 3.—Low frequency tracing at the apex. Normal subject (24 years of age). Systolic depression (predominance of volume changes).

Regional Variations.—

1. *Pulmonic area*: The waves are usually small, but amplification facilitates their study. There is a relatively high presystolic wave and a well-defined positive wave during early systole (Fig. 4,*A*). The former is probably due to contraction of the left atrium, indirectly transmitted through intermediate organs. Whenever there is a pulsation during the ejection period, this is caused by the pulse of the pulmonary artery.

2. *Aortic area*: The waves are usually small. There is a well-defined wave during the tension period and a positive wave during early systole. The former is transmitted from the left ventricle; the latter is an arterial wave caused by the pulse of the ascending aorta. Closure of the aortic valves is marked by a notch (Fig. 5,*C*).

3. *Tricuspid area*: The cardiogram shows a high presystolic wave, small systolic notches, and a well-defined, early diastolic wave. The first is probably due to the contraction of the right atrium because of the proximity of this chamber; the latter is due to rapid inflow into the right ventricle.

4. *Suprasternal notch*: A single, large systolic wave is recorded over this area. This is caused by the pulse of the aortic arch, transmitted through the structures of the upper mediastinum. Closure of the semilunar valves is very apparent in the descending limb of the curve.

It is suggested that appropriate names be given to the various waves of the cardiogram, so that their recognition may be simplified. The positive wave of rapid filling should be called 3 (third sound). The small wave, present at the time of atrial contraction, should be called 4 (fourth sound). The small wave terminating the tension period should be called 1a; the larger one terminating the

ascending phase, 1b. The small rebound ending systole should be called 2a. The drop which precedes rapid filling should be called 2b (opening of the atrioventricular valves). Last, the wave of arterial type which may be recorded over the aortic and pulmonary areas should be called p (pulse).

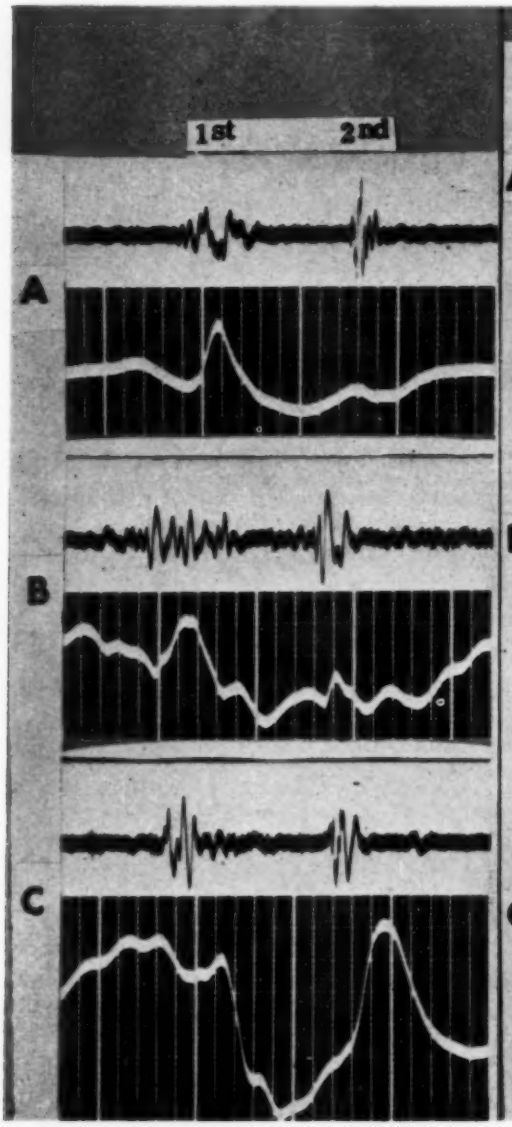

Fig. 4.

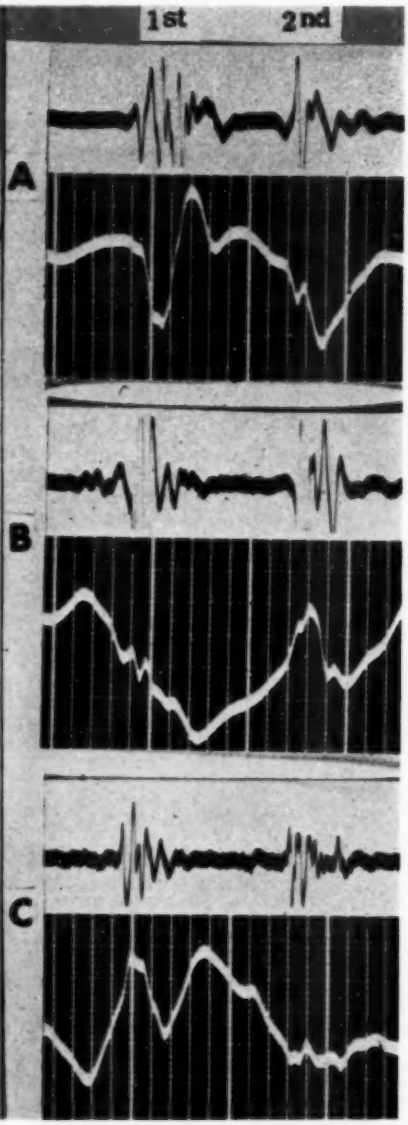

Fig. 5.

Fig. 4.—Regional tracings in a normal young man. *A*, Pulmonic area; *B*, epigastric tracing; *C*, hepatic tracing (at right hypochondrium).

Fig. 5.—Regional tracings in a subject with functional murmur. *A*, Apex; *B*, midprecordium; *C*, aortic area.

Normal Epigastric Tracing.—The following factors should be considered:

1. Pulsations transmitted through the diaphragm from the heart, mainly the right heart.

2. Effect of changes of intrathoracic pressure on the diaphragm.
3. Pulsations of the liver.
4. Pulsations of the abdominal aorta.

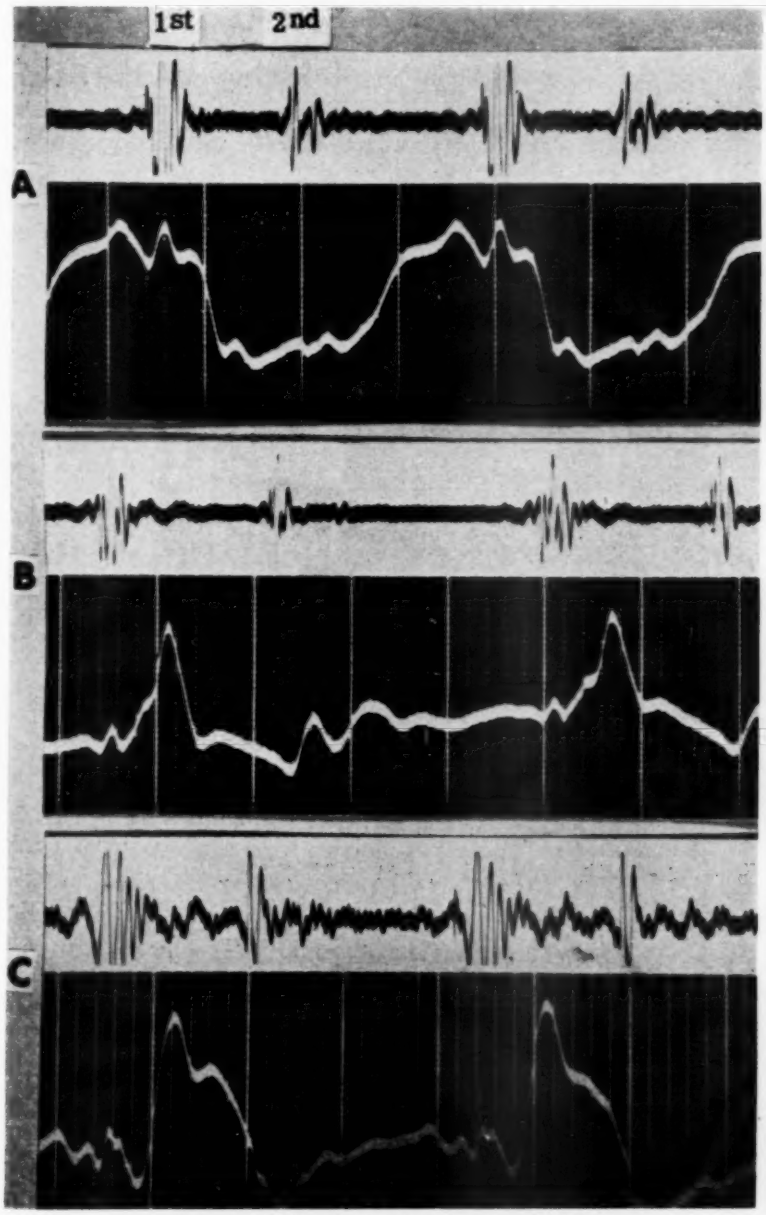

Fig. 6.—Epigastric tracings in normal subjects.

Epigastric tracings are by no means identical. Even in different normal individuals, an amazing variety of records can be obtained. However, these tracings can be classified in four groups, two of them common, the others less so (Fig. 6). Some parts of the tracing are common to all while others vary. Again, a terminology similar to that of the cardiogram is suggested.

A high positive wave is usually present during presystole (wave 4). During the period of tension, the curve either falls below the base line or has two small notches caused by the two valvular events of this phase (1a and 1b). A positive wave may be present in the phase immediately following. However, in most tracings, a deep negative plateau takes place during a large part of systole. (Fig. 6, *A*.) A positive wave, simultaneous with the arterial pulse, occurs in others (wave p). (Fig. 6, *C*.) Closure of the semilunar valves is marked on all records by a well-defined notch (2a) which may be either upright or inverted. The opening of the atrioventricular valves is well defined in most records (2b). The rapid filling of the ventricles is also indicated by a deep wave which may be either upright or inverted (wave 3). (Fig. 6, *B*.)

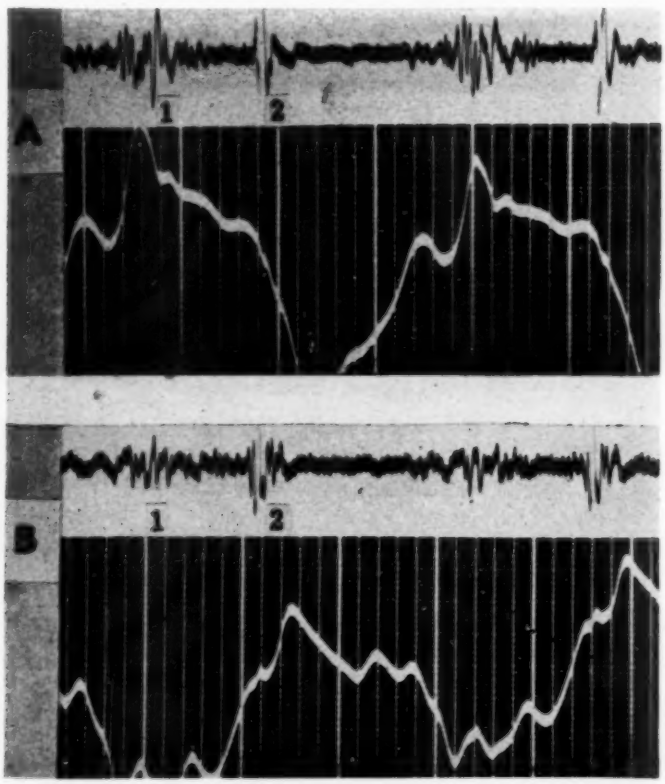

Fig. 7.—Hypertensive and coronary heart disease. Patient was 56 years old. Predominance of left ventricle; large artial wave. *A*, Apex; *B*, epigastrium.

The presystolic wave is largely due to the mechanical movement of the right atrium, transmitted through the diaphragm. The two notches 1a and 1b, when present, are caused by the valvular events of early systole and probably more by those of the right heart. The high systolic wave represents the beginning of a systolic plateau, abruptly interrupted by the following systolic collapse. It is likely that the plateau is due mostly to motion of the right ventricle; the collapse, to its volume changes. The high wave of other tracings, on the contrary, occurs later and is a transmitted aortic pulsation.

Four different types of tracings can be recognized.[13] Type 1 tracings reveal the predominant influence of ventricular events during systole and early diastole. Type 2 tracings show mainly the effect of changes of intrathoracic pressure (Fig. 5,*A*). Type 3 tracings are largely influenced by the aortic pulsations but still show effect of motion during presystole and early systole and effect of thoracic pressure changes during diastole (Fig. 6,*C*). Type 4 tracings are pure hepatic tracings and occur when the enlarged liver occupies the epigastrium (identical with that of Fig. 4,*C*).

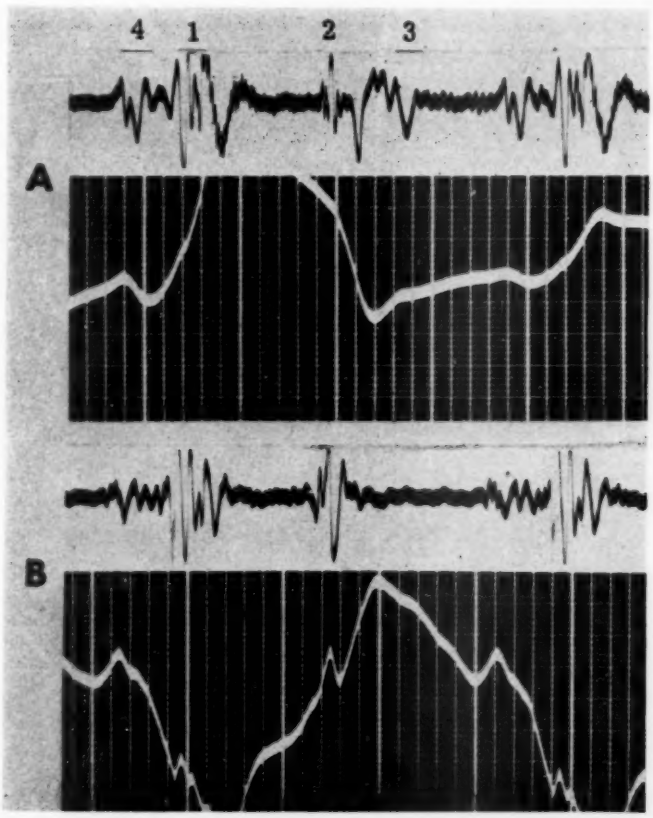

Fig. 8.—Predominance of left ventricle. *A*, Apex; *B*, epigastrium. Coronary heart disease; posterior myocardial infarction. Patient was 89 years old.

The Patterns of Ventricular Enlargement.—A comparison between the tracings recorded at the apex and those recorded at the epigastrium indicates three typical patterns.

The *first pattern* is revealed by a high systolic pulsation at the apex. This pulsation may assume the aspect of a plateau lasting during the entire systole or that of a high, peaked wave during early systole, followed by a depression during the second half of systole. In these cases, the epigastric tracing reveals a deep depression during most, or all, of systole. The combination of a positive wave at

the apex with a negative wave at the epigastrium may be interpreted as being due to a dynamic preponderance of the left ventricle, caused by dilatation or hypertrophy (Figs. 7 to 9).

The *second pattern* is revealed by a high positive wave of the epigastric tracing during the first half of systole. At the same time, the tracing of the apex reveals a deep depression during the entire systole.* This pattern may be interpreted as being due to exclusive or predominant enlargement of the right ventricle caused by dilatation or hypertrophy (Fig. 10).

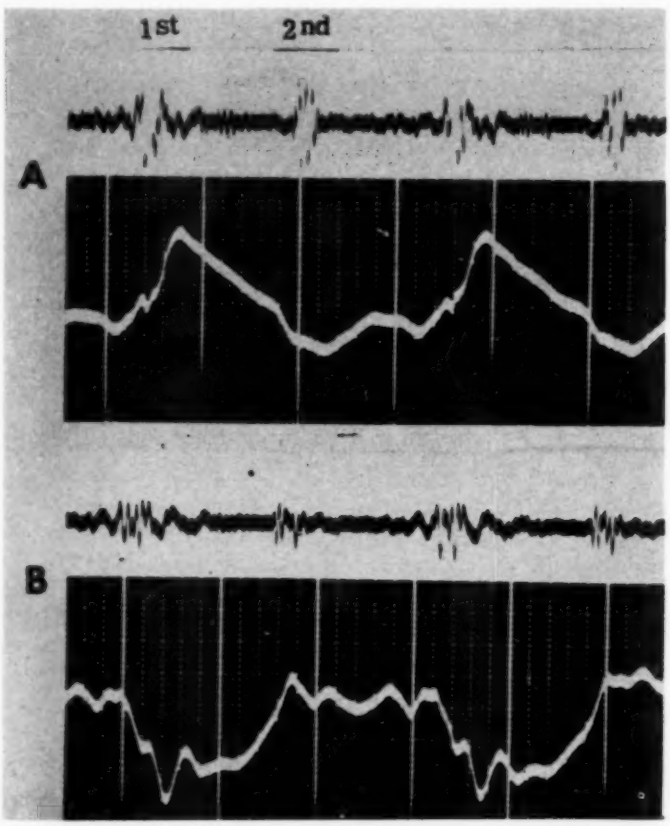

Fig. 9.—Left ventricular preponderance in a 12-year-old patient with aortic and mitral lesions. *A*, Apex; *B*, epigastrium.

The *third pattern* is less common and is revealed by a positive thrust both at the apex and the epigastrium. This may be interpreted as the result of simultaneous enlargement of both ventricles causing extensive contact of the heart both with the chest wall and the diaphragm (Fig. 11).

*In order to be reliable, the apical tracing has to be taken with the funnel over the point of maximum impulse. It may happen (like in certain cases of aortic insufficiency) that a positive impulse at the apex is accompanied by depression around the apex; a record taken near but not at the apex may reveal a depression instead of a positive thrust.

1. *Left ventricular preponderance*: The pattern of left ventricular preponderance was found in several groups of patients. It was shown by three out of six cases of mitral insufficiency (50 per cent); one out of six patients with mitral stenosis (16.6 per cent); two out of ten with double mitral defect (20 per cent); three out of five with mitral and aortic lesions (60 per cent); and three out of twelve with defects of the three valves (25 per cent). As shown by the above figures, a left ventricular preponderance is most common in those cases having a lesion of both the mitral and the aortic valve (60 per cent) followed by those with predominant insufficiency of the mitral valve (50 per cent). The same pattern of left ventricular preponderance was found in the single case with syphilitic heart disease which was completely studied; in three out of six cases of congenital heart disease (all of them having interventricular septal defect) (50 per cent); and in eleven out of eighteen patients with hypertensive heart disease (61.1 per cent). The same pattern was also found in four out of seven cases of coronary heart disease, all of them with left bundle branch block.

Thus, left ventricular preponderance was found commonly in hypertensive hearts, syphilitic heart disease, interventricular septal defect, left bundle branch block, and rheumatic lesions causing enlargement of the left ventricle.

A good correlation was found between pattern 1, electrocardiographic evidence of ventricular preponderance (left axis shift, left ventricular hypertrophy), and roentgenologic evidence of enlargement of the left ventricle.

2. *Right ventricular preponderance*: The pattern of right ventricular preponderance was found only in one out of six cases of mitral insufficiency (the patient was in severe congestive failure). It was found in ten out of twenty cases of mitral stenosis (alone, or associated with mitral or aortic insufficiency) (50 per cent). The same pattern was found in four out of ten cases of defects of the three valves (40 per cent). Right ventricular hypertrophy was also found in six out of twenty cases of coronary heart disease (out of three patients with right bundle branch block, two had this pattern), in four out of eighteen cases of hypertension (22.2 per cent), and in all three cases of chronic cor pulmonale (100 per cent).

Therefore, right ventricular preponderance was found most commonly in chronic cor pulmonale, followed by mitral stenosis and multiple valvular defects. It was present in a smaller percentage of cases of coronary or hypertensive heart disease, or in mitral insufficiency, whenever there was a right heart failure.

3. *Total cardiac enlargement*: Pattern 3, due to simultaneous enlargement of both ventricles, was found in sixteen cases: four cases of hypertensive heart disease; seven cases of mitral valve lesions; one case of intraventricular septal defect, and four cases of combined valvular lesions (mitral and aortic or trivalve defects).

A good correlation between this complex pattern and roentgenologic evidence of total cardiac enlargement was found in all cases where x-ray documents were available.

The Diastolic Waves in the Various Tracings.—

1. *Atrial wave*: The interval between right and left atrial contractions is so small in normal individuals that very little difference in the time of appearance

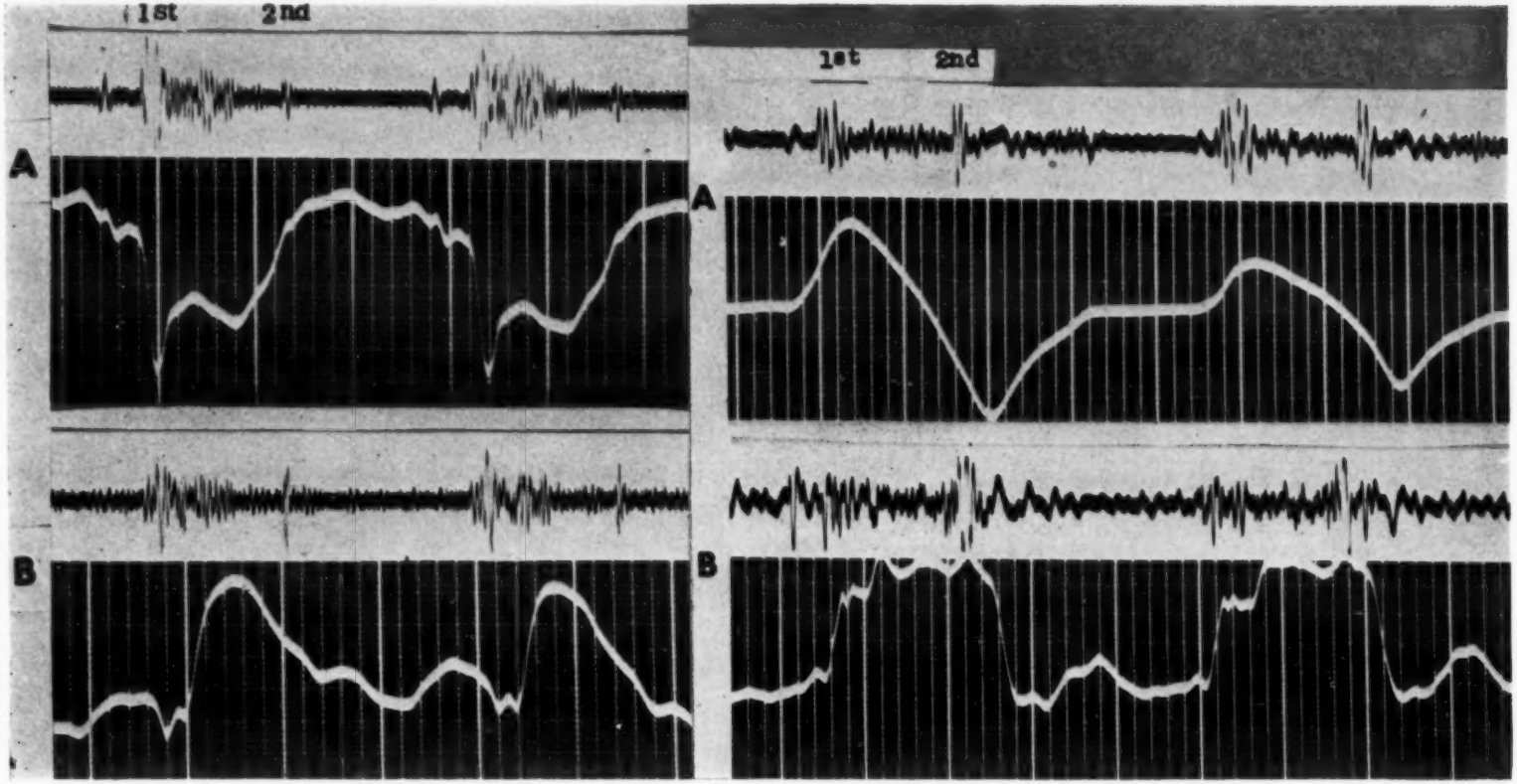

Fig. 10.

Fig. 11.

Fig. 10.—Predominance of right ventricle. Large atrial sound. Double mitral defect. *A*, Apex; *B*, epigastrium.

Fig. 11.—Enlargement of both ventricles with predominance of the right. Double mitral defect, tricuspid insufficiency, and aortic stenosis. *A*, Apex; *B*, epigastrium.

of the waves is to be expected. Even so, a marked difference can be found between apex and epigastrium (Fig. 12). On the contrary, patients with fibrosis of the atrial myocardium are more apt to give evidence of increased delay between right and left atrial contraction. Studies made on such patients have proved the following data:

A. Tracings recorded over the second right intercostal space frequently show left atrial contraction as a downward wave. Tracings recorded over the second left intercostal space frequently show it as a high positive wave.

B. Tracings of the apex usually show a positive wave for left atrial contraction, sometimes preceded by a negative wave for right atrial contraction.

C. Tracings of the epigastrium show mainly the effect of right atrial contraction which is revealed by a high positive wave. Sometimes a negative phase follows this at the time of left atrial contraction.

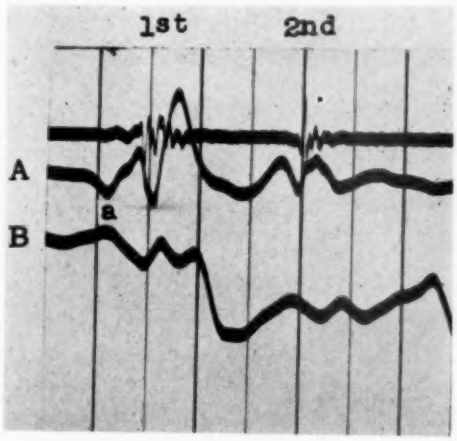

Fig. 12.—Normal subject. Positive right atrial wave (*a*) at the epigastrium (*B*) coinciding with a negative wave at the apex (*A*).

The tracings of the apex and epigastrium seem to show the effect of presystolic filling of the respective ventricle while the waves recorded at the base seem due to indirect transmission of the atrial waves.

The atrial wave (wave 4) presented good development and an unusual height in certain types of patients. A large atrial wave in the second and third left intercostal spaces was found in most cases of rheumatic heart disease with mitral lesions or mitral plus aortic defects. A large atrial wave in the epigastric tracing was found in all cases of cor pulmonale. In two of them, the atrial wave of the epigastric tracing was much larger than that of the apical tracing while, in the third, the two waves were equivalent.

In four cases of atrioventricular block, the atrial waves were high both at the epigastrium and at the apex. In all, the atrial waves were far more pronounced in the low frequency tracings than in the phonocardiogram (Fig. 13).

2. *Wave of rapid filling*: The wave of rapid filling (wave 3) may present typical changes. In a large percentage of cases of mitral stenosis (eight out of

twelve), the wave 3 was very low and was poorly defined. This indicates slow filling of the left ventricle due to mitral obstruction (Fig. 14,*A*).

Apical Tracings of Aortic Patients.—As previously revealed by inspection and palpation, two typical patterns are found in aortic patients:

1. *Pattern of aortic insufficiency*: There is a high rounded wave in systole (Fig. 14,*B*). An early peaked wave may be followed by a drop during the second part of the ejection phase. This high wave was noted by old French clinicians and called "choc en dôme." It should be noted that a systolic negative wave is frequently recorded near the apex.[15] Left ventricular hypertrophy and rapid outflow of blood from the chest are responsible for these data. A high pulsation is also frequently recorded in these patients over the second right intercostal space and at the suprasternal notch (Fig. 15).

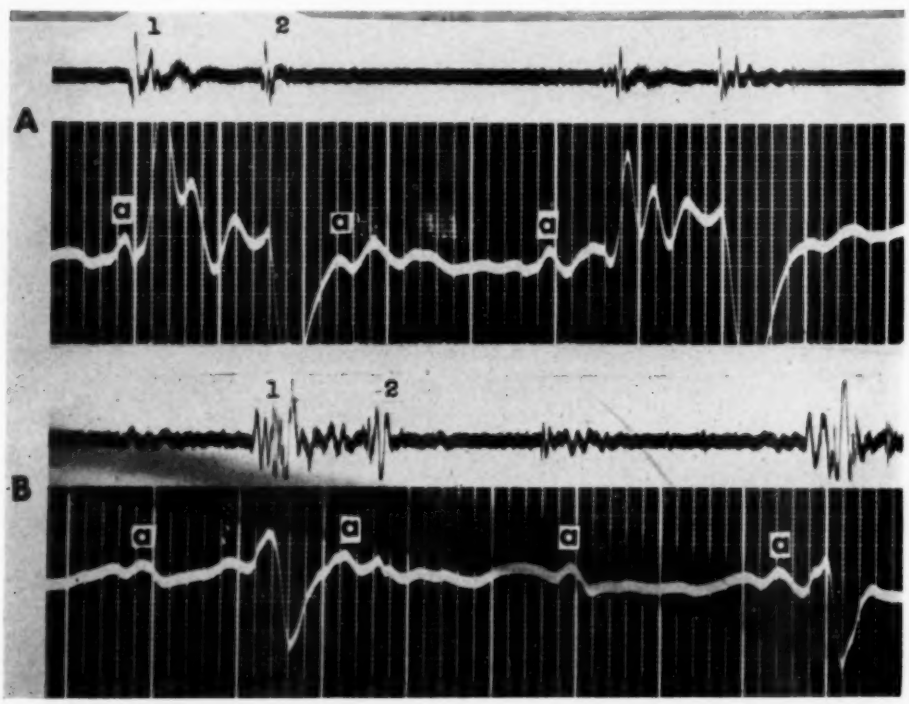

Fig. 13.—Atrial waves in two cases of complete atrioventricular block. *A*, Apex; *B*, epigastrium.

2. *Pattern of aortic stenosis*: There is a slow rise, a notched or staggered systolic plateau, and a slow descent (Fig. 14,*C*). Left ventricular hypertrophy and obstruction at the aortic valve are responsible for these data.

Tracings of Constrictive Pericarditis and Tricuspid Lesions.—Cases with adhesive or constrictive pericarditis and those presenting a systolic snap due to the tension of adhesion may present interesting cardiograms. In three cases out of seventeen, there was coincidence between a systolic snap and an additional wave in the low frequency tracing of the apex. In six cases out of seventeen,

there was systolic retraction at the apex or unusual configuration of the tracing: early retraction followed by positive thrust during early systole, or irregular and bizarre configuration of the tracing (Fig. 16).

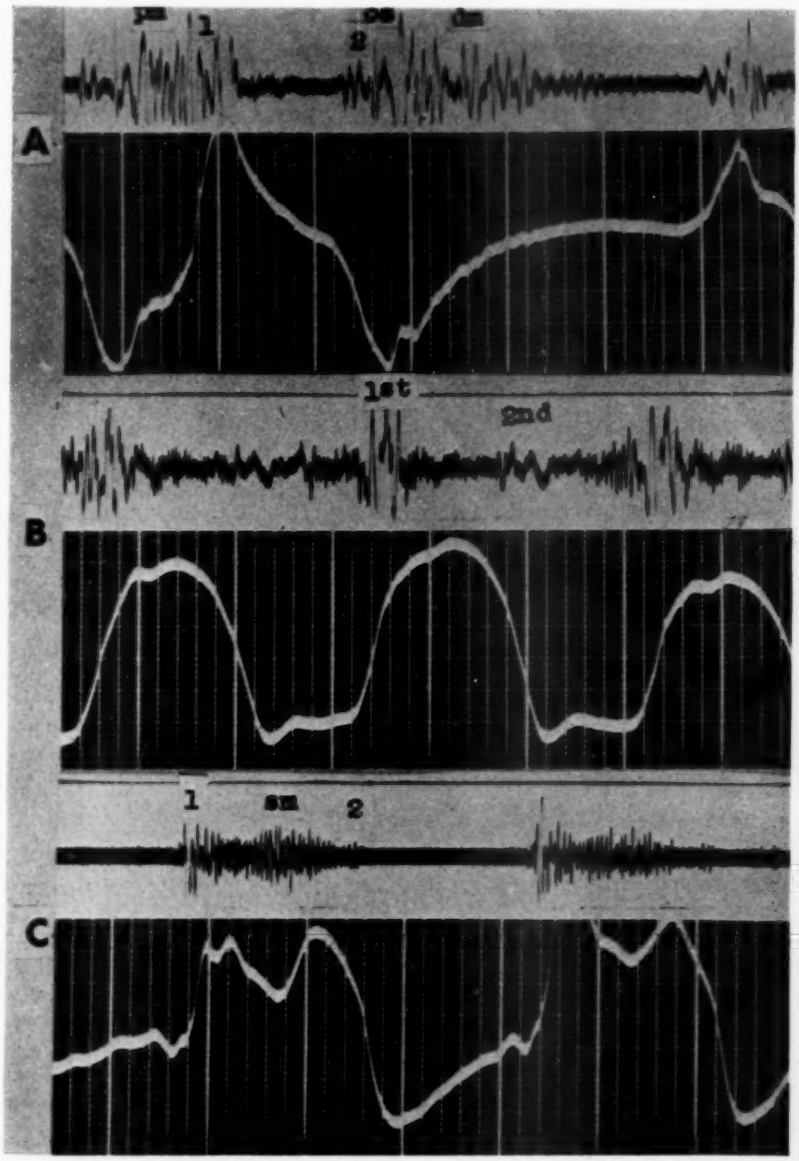

Fig. 14.—Low frequency tracings at the apex in: (*A*) mitral stenosis; (*B*) aortic insufficiency, and (*C*) aortic stenosis.

A typical seesaw movement was observed in several cases with tricuspid insufficiency or constrictive pericarditis. Both presented a negative wave in systole at the apex. However, the tricuspid patients presented a positive systolic wave at the epigastrium and right hypochrondrium (pattern of right ventricular

enlargement plus expansive hepatic pulsation) (Fig. 17), while the pericardial patients presented this positive systolic wave at the right side of the chest (forward thrust due to elastic rebound of the ribs). These tracings confirm previous observations of Dressler[15] by means of palpation.

Tracings in Bundle Branch Block.—The low frequency tracings were studied in twelve cases of bundle branch block, eight cases of right and four of left bundle branch block (Figs. 18 and 19).

Fig. 15.

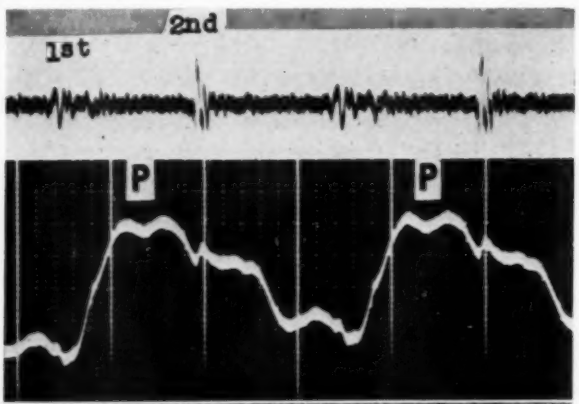

Fig. 16.

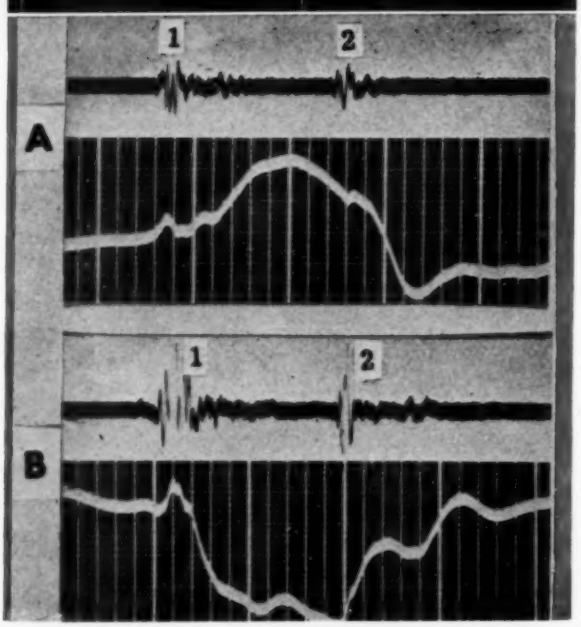

Fig. 15.—Strong aortic pulsation at the second right intercostal space (*P*) in a patient with aortic insufficiency.

Fig. 16.—Seesaw movement in adhesive pericarditis. *A*, Third right intercostal space; *B*, apex. Retraction of the apex.

In spite of a notable variability of configuration, certain features were frequently observed. In left bundle branch block, a high, large pulsation was frequently observed in the apical tracing while the tracing of the epigastrium had a

systolic depression. In right bundle branch block, the tracing of the apex frequently showed a short and rapid positive thrust followed by a return to the isoelectric line while the epigastric tracing showed a short negative wave followed by a positive plateau.

These results can be easily explained by considering that bundle branch block of one side frequently coincides with enlargement of the ventricle of the same side, as proved by Master and associates.[19] In left bundle branch block, the enlarged left ventricle contracts late and causes a high, sustained apical wave. In right bundle branch block, the enlarged right ventricle contracts late and causes a high but delayed positive wave at the epigastrium.

CONCLUSIONS

Low frequency tracings, recording the slow pulsations of the chest and abdomen, were studied in 250 cases. This included twenty-eight normal subjects and a variety of cardiac cases. The tracings were recorded at the apex in all cases, at the apex and epigastrium in 105 cases, and over various areas of the precordium in 108 cases. Following demonstration of the similarity between the results obtained with two methods, that making use of an electromanometer and that employing a crystal microphone with a linear response, the latter was selected.

The complex motions of the apex were first investigated. The normal tracing presents several variants; one consists of a positive systolic plateau; another, of a single or double peak followed by a deep depression during the ejection phase. A negative wave during the isometric relaxation phase and a positive wave during rapid filling are nearly constant. They represent an important part of the tracing for timing certain diastolic extra sounds, like the opening snap and the third heart sound.

Movements of the heart, changes of cardiac volume, and arterial pulsations contribute to the low frequency tracings but the part played by these three factors varies according to the size and position of the heart and to the location of the funnel.

The regional variations of the tracing have a certain importance. The details of the various tracings (pulmonic, aortic, tricuspid, and suprasternal) have been studied in order to find out whether one or the other was superior in special cases by revealing the motions of certain cardiac chambers or of the large vessels. It was concluded that the aortic and suprasternal tracings are influenced by aortic pulsations; the pulmonic, although to a lesser extent, by pulmonic pulsations and by left atrial contractions; the tricuspid, by right atrial and right ventricular contractions; and the apical and midprecordial, by left ventricular contractions.

A study of the presystolic atrial wave revealed that right atrial contraction is revealed by a positive wave at the epigastrium while left atrial contraction is revealed by a positive wave over the second and third left intercostal spaces, and sometimes at the apex.

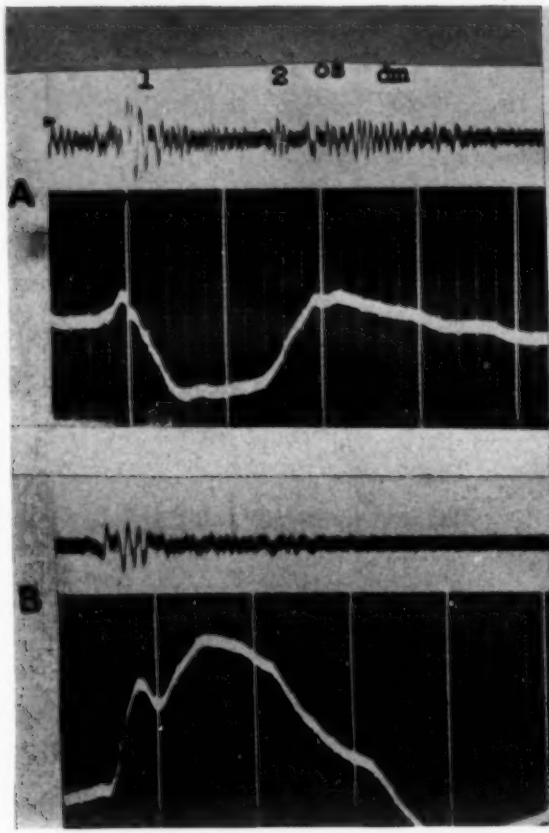

Fig. 17.

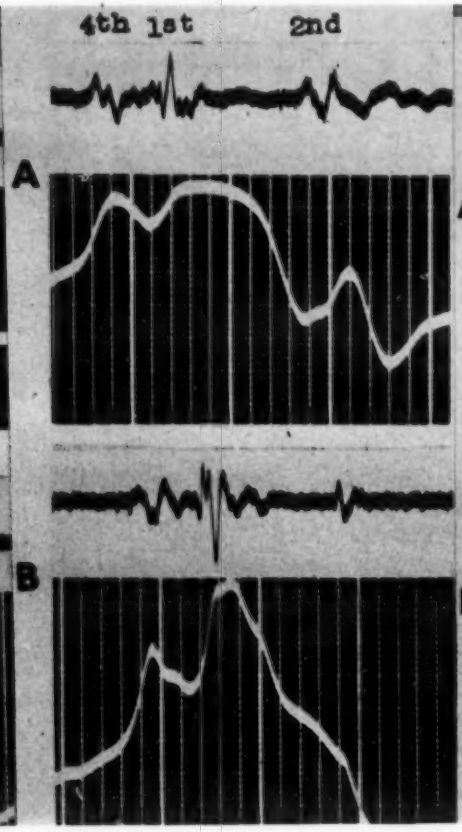

Fig. 18.

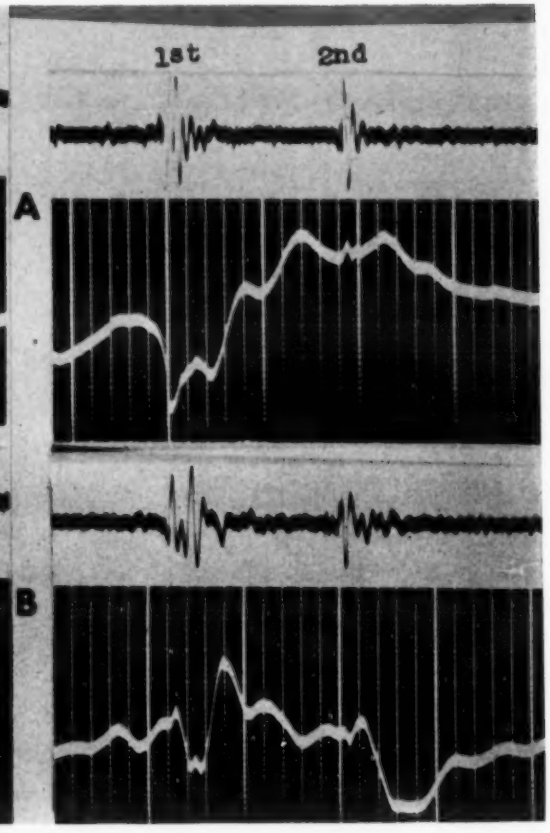

Fig. 19.

Fig. 17.—Right ventricular preponderance in a case of mitral, aortic, and tricuspid lesions. *A*, Apex; *B*, epigastrium. The positive wave recorded at the epigastrium is probably of hepatic origin (expansive pulsation of the liver).

Fig. 18.—Left bundle branch block. *A*, Apex; *B*, epigastrium.

Fig. 19.—Right bundle branch block and anterior myocardial infarct. Patient was age 55. *A*, Apex; *B*, epigastrium.

Appropriate names have been suggested for the various waves, so that comparison can be made between the various tracings.

The epigastric tracing presents four types of tracings. One of them is a pure aortic tracing, another is a pure hepatic tracing, while two others are the main variations to be considered.

Ventricular enlargement manifests itself by three patterns resulting from comparison of the apical with the epigastric tracing. Left ventricular enlargement is revealed by a positive plateau at the apex and by a negative wave at the epigastrium. Right ventricular enlargement is revealed by a short positive wave followed by a negative wave (or by a negative plateau) at the apex while the epigastrium presents a positive plateau. Enlargement of both ventricles may cause positive waves in both areas.

The tracings recorded in bundle branch block are similar to those recorded in cases of ventricular hypertrophy. However, influence of the contraction of the delayed ventricle was revealed by several tracings, so that a diphasic or bizarre tracing is possible.

Special features of the low frequency tracing were noted in cases with tricuspid insufficiency and constrictive pericarditis, as well as in patients with mitral stenosis, aortic insufficiency, and aortic stenosis.

Fig. 19.—Right bundle branch block and anterior myocardial infarct. Patient was age 55. *A*, Apex; *B*, epigastrium.

SUMMARY

Low frequency tracings were studied in 250 cases including twenty-eight normal subjects. The tracings were recorded at the apex in all cases, at the apex and epigastrium in 105 cases, and over various precordial areas in 108 cases.

Description of the typical pattern and of the possible variants is given for the various tracings. The waves are interpreted as being due to a combination of motion and volume changes of the cardiac chambers plus transmitted pulsations of the large vessels.

Appropriate nomenclature is given to the various waves.

Regional cardiograms are of interest in the study of the atrial and arterial waves. Cardiograms at the apex and epigastrium are of interest in the study of ventricular hypertrophy and in bundle branch block.

The patterns due to either right or left ventricular enlargement and to bilateral enlargement are described.

Of special interest are the cardiograms of cases with tricuspid insufficiency and constrictive pericarditis.

The systolic part of the apical tracing presents typical changes in aortic insufficiency and aortic stenosis. The diastolic part of the apical tracing presents typical changes in mitral stenosis.

REFERENCES

1. Marey, E. J., and Potain: La méthode graphique dans les sciences éxpérimentales, ed. 2, Paris, 1885, Masson & Cie.
2. Cushney, E.: Quoted by Weber.[5]
3. Hess, C.: Untersuchung der Bewegungen des normalen und pathologischen Herzens, sowie der zentralen Gefaesse, mit der Frankschen Apparat, Ergebn. d. inn. Med. u. Kinderh. **14**:370, 1915.

4. Weitz, W.: Ueber die Kardiographie am gesunden und pathologischen Herzen, Ergebn. d. inn. Med. u. Kinderh. **22**:418, 1922.
5. Weber, A.: Die Elektrokardiographie und andere graphische Methode in der Kreislaufdiagnostik, Berlin, 1926, Julius Springer.
6. Pachon, V., and Fabre, R.: Le cardiogramme de decubitus lateral gauche en clinique, Paris, 1929, Gastron Doin & Cie.
7. Lewis, J. K.: Nature and Significance of Heart Sounds and of Apex Impulses in Bundle Branch Block, Arch. Int. Med. **53**:741, 1934.
8. Wolferth, C. C., and Margolies, A.: Asynchronism in Contraction of the Ventricles in the So-called Common Type of Bundle Branch Block: Its Bearing on the Determination of the Side of the Significant Lesion and on the Mechanism of Split First and Second Heart Sounds, Am. Heart J. **10**:425, 1935.
9. Battro, A., Braun-Menendez, E., and Orias, O.: L'asynchronisme ventriculaire dans les blocs de branche. Sa demonstration au moyen de l'enregistrement des phenomenes mécaniques de l'activité cardiaque, Arch. d. mal. du coeur **31**:250, 1938.
10. Viciu, E.: Sur la valeur pathognomonique des modifications du cardiogramme dans le diagnostic des cardiopathies congenitales, Cardiologia **15**:36, 1950.
11. Miller, A., and White, P. D.: Crystal Microphone for Pulse Wave Recording, Am. Heart J. **21**:504, 1941.
12. Rappaport, M. B., and Sprague, H. B.: The Graphic Registration of the Normal Heart Sounds, Am. Heart J. **23**:591, 1942.
13. Mackenzie, J.: The Study of the Pulse, Arterial, Venous and Hepatic and of the Movements of the Heart, New York, 1902, The Macmillan Company.
14. Lang, G.: Ueber einige durch die Herzaktion verursachten Bewegungen der Brustwand und des Epigastriums, Deutsches Arch. f. klin. Med. **108**:35, 1912.
15. (a) Dressler, W.: Die Brustwandpulsationen als Symptome von Heraz- und Gefaesskrankheiten, Wien, 1933, Wilhelm Maudrich.
    (b) Dressler, W.: Pulsations of the Wall of the Chest, Arch. Int. Med. **60**:225, 437, 441, 654, and 663, 1937.
16. Fukui, N.: Ueber die epigastrische Pulsation, Wein. Arch. f. inn. Med. **15**:349, 1928.
17. Luisada, A. A.: Heart. A Physiologic and Clinical Study of Cardiovascular Diseases, Baltimore, 1948, Williams & Wilkins Company.
18. Johnston, F. D., and Overy, D. C.: Vibrations of Low Frequency Over the Precordium, Circulation **3**:579, 1951.
19. Master, A. M., Kalter, H., Dack, S., and Jaffe, H. L.: The Relation Between Bundle Branch Block and Cardiac Enlargement, Am. Heart J. **20**:186, 1940.

OBSERVATIONS ON THE ELASTICITY OF THE PULMONARY VASCULATURE IN MAN*

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EXTRAORDINARILY little is known of the physical properties of the human cardiopulmonary vasculature, particularly during life. The most obvious approach to a study of this problem would be to correlate the cardiac output with the pulmonary arterial pressure or with the pulmonary arteriocapillary pressure gradient. Unfortunately there is not presently available a means of rapidly, repeatedly, and accurately measuring the cardiac output, while the errors in measuring central pressures are well known. Furthermore, we have been unable to show any relationship between these two parameters in normal subjects in whom the blood flow or the pulmonary arterial pressure was acutely altered. It has, therefore, occurred to us that another approach to the problem might be an examination of the relationship between the mean velocity and the minute volume of blood flow through the cardiopulmonary circuit and the degree of distention of this circuit, that is, the pulmonary blood volume. The recently revived dye-dilution method of measuring the cardiac output makes possible such an approach.

METHODS

The subjects of these measurements were a heterogeneous adult hospital population. The majority were considered to have relatively normal cardiovascular systems. Included, however, were many individuals with a high cardiac output as well as others with low-output congestive heart failure.

The Stewart-Hamilton method of measuring the cardiac output as modified by Ebert was used. Our experience with this technique has been reported elsewhere in detail.[1] A carefully measured amount of the blue dye T-1824 was injected through a Cournand catheter into the main pulmonary artery. During the first circulation of the dye, rapidly consecutive blood samples were collected from a needle lying in a peripheral artery. The dye content of these samples was measured spectrophotometrically and a time-concentration curve was con-

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Received for publication July 3, 1952.

*This study was supported in part by a grant from the American Heart Association and in part by Contract N9onr92500, Office of Naval Research, Project Designation No. NR 112-607.

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structed on semilogarithmic paper. The cardiac output was calculated from the degree of dilution of the dye. The mean circulation time from the pulmonary to the peripheral artery was obtained by a simple graphic integration of the dye curve. The volume of blood moving between the catheter tip and the arterial needle is the product of the mean circulation time in seconds and of the blood flow per second. This is considered to be a gross index of the pulmonary blood volume, although the left heart and the proximal arterial tree are included in the measurement.

RESULTS

Fig. 1 is a scatter plot in which the cardiac output and the mean circulation time are related. Three hundred forty-three such measurements in 287 subjects are represented. A statistical analysis of these data yielded a hyperbolic regression as the simplest line of best fit (Fig. 2).*

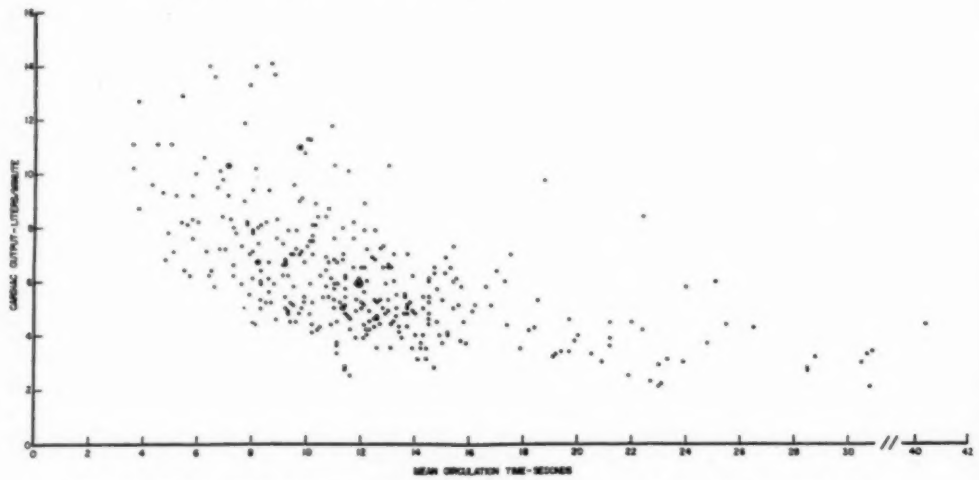

Fig. 1.—Relationship between cardiac output and mean circulation time in 287 subjects.

This biologic cross section was then compared with various rigid systems. In a rigid system, of course, the volume remains constant at all rates of flow while the mean velocity and the minute volume of flow vary reciprocally. Reciprocal,

*The 343 measurements were first visually coded to 111 weighted subgroups, with a 0.23 per cent mean error resulting. The data were then analyzed for the best fitting rectangular hyperbola and for polynomials of the first, second, and third degree. The correlation indices of the third degree polynomial and hyperbola were both acceptable, but the hyperbola was chosen because of its obvious better fit near the extremities of the original data:

TYPE OF CURVE	CORRELATION INDEX	EQUATION
Linear	0.582	$Y = 9.35 - 0.258\ x$
Rectangular Hyperbola	0.716	$Y = \frac{29}{x} - 0.666$

Y = Cardiac output in liters/minute.
x = Mean circulation time in seconds.

that is, pure hyperbolic, curves for rigid systems of different volumes in the observed range of the pulmonary blood volume were calculated (Fig. 3).

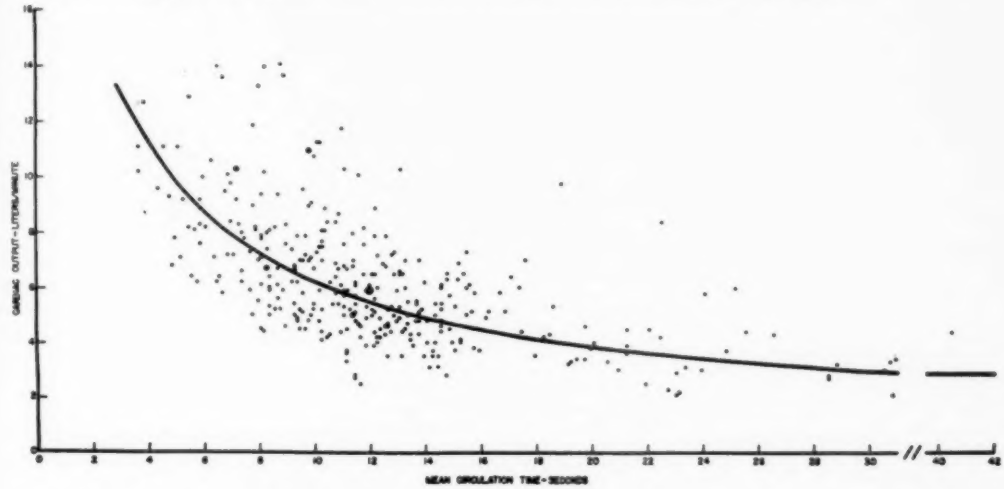

Fig. 2.—Relationship between cardiac output and mean circulation time in 287 subjects.

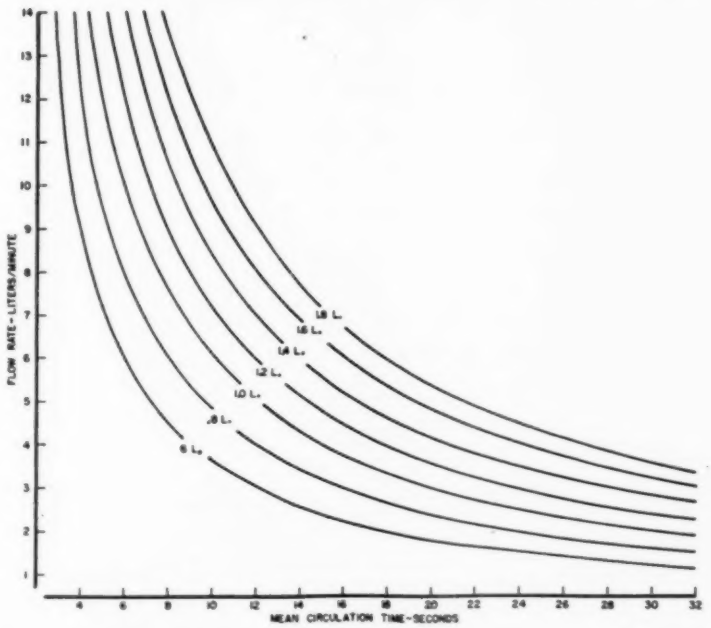

Fig. 3.—Relationship between flow and mean circulation time in rigid systems of different volumes.

Finally, possible changes in the relationship between the mean circulation time and the cardiac output were investigated in individuals in whom the cardiac output was acutely altered. A broad spectrum of cardiac output, ranging from the high output of thyrotoxicosis to the low output of irreversible congestive heart failure, was represented. The alterations of blood flow were induced by the

application of venous occluding tourniquets to the thighs, phlebotomy, passive footward tilting, anoxia, injection of epinephrine and aminophylline, release of arterial tourniquets, and exercise. A scatter plot relating the cardiac output and the mean circulation time was constructed. One hundred seventy-six multipoint observations in eighty-two subjects were available for this plot. Lines were drawn connecting the control points with those observed after the cardiac output had been altered. A series of slopes was thus defined. The regression of each slope was calculated. Average values for these slopes are depicted in Fig. 5 by the series of dotted lines which are superimposed on the curves shown in Figs. 2 and 3.*

COMMENT

It is necessarily assumed in this discussion that alterations of the pulmonary blood volume found with a normal or an elevated cardiac output occur in the lungs, and not in the left heart-arterial segment. A considerable justification for this assumption rests on cineangiographic observations made in this department.

Inspection of Fig. 4 shows that in the range of normal resting cardiac output the biologic regression line deviates markedly from that characteristic of a simple rigid system. Furthermore, if the blood flow be acutely altered, the relationship of the mean circulation time to the cardiac output is not reciprocal, as is shown by the relatively blunt angle of intersection of the broken with the solid lines. It is in this area that a considerable change in the central pressures can be effected without correspondingly large changes in the cardiac output, or vice versa, as has been reported from this laboratory.[2,3] Therefore, it may be concluded that at resting rates of blood flow in normal individuals the pulmonary vasculature behaves as a simple elastic system.

At high flow rates, however, it is seen that the regression lines for the biologic and the rigid systems are parallel. Therefore, an acutely induced increase or decrease of cardiac output shows an insignificant deviation from the regression lines characteristic of rigid systems. In this area of high flow rates, the pulmonary pressures vary directly with the cardiac output, as shown by Dexter and associates.[4] Here it may be concluded that the pulmonary vasculature tends to behave as a rigid system.

At critically low flow rates, the regression lines for the biologic and the rigid systems likewise are essentially parallel. In this range the cardiac output tends to be fixed. The data show an anomaly which may be described as follows: If the perfusion pressure and the rate of flow through an artificial elastic system be reduced, the volume of the system decreases. It is observed in the biologic system, however, that at very low flow rates the pulmonary blood volume tends to increase. This apparent anomaly is due probably to dilatation of the left atrium and of the left ventricle.

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*For any arbitrary length on a trend line: Let x = the mean circulation time projection and Y = the cardiac output projection. (Assign Y the sign of the particular slope involved; that is, for a negative slope let Y be negative.) Then: The mean slope, $M = \frac{\Sigma Y}{\Sigma x}$. The mean slope is thus calculated for various groups of regressions, and from this information calculation of the slope at any point may be made by graphical techniques. Representative mean values for these regressions are shown by the dotted lines in Fig. 4.

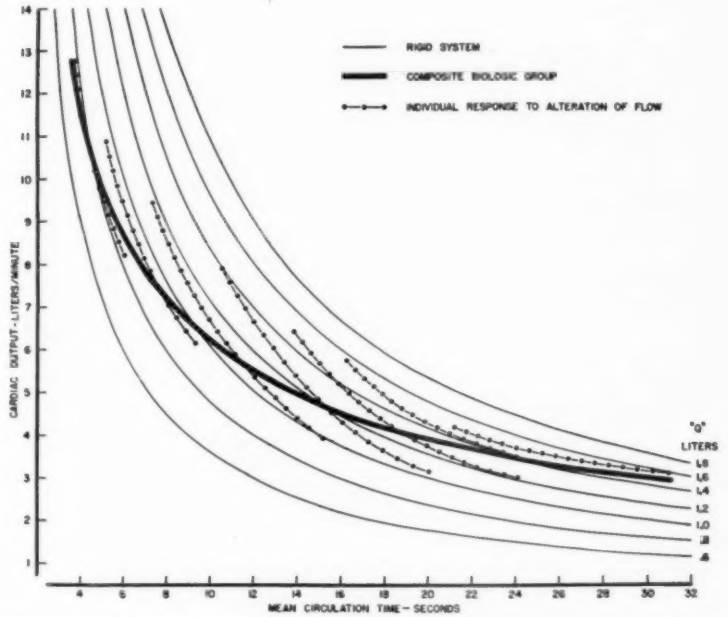

Fig. 4.—Interrelationship of flow, mean circulation time, and "Q" in biologic and rigid systems.

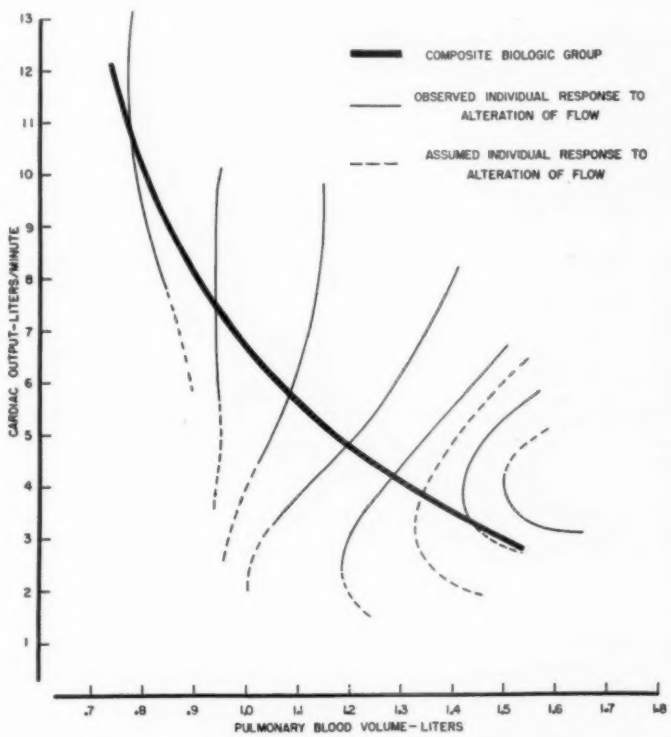

Fig. 5.—"Elasticity" of pulmonary vasculature related to blood flow.

The presentation of these data in another fashion shows graphically how the pulmonary vascular elasticity changes with changes in the cardiac output. In Fig. 5 the pulmonary blood volume has been calculated from the data in Fig. 4 for widely varying rates of blood flow. It is evident that with a high cardiac output the pulmonary blood volume is relatively constant, as in a rigid system. In the range of normal resting cardiac output, however, the pulmonary blood volume tends to vary with the blood flow, as would be expected in an elastic system. At very low rates of flow, the data are rather meager but could be interpreted as overstretching and dilatation, presumably of the left heart. A provocative but highly speculative possibility suggested by the inflection of these latter curves is that, at a critical reduction in the blood flow, there may be a striking change in the physical characteristics of the pulmonocardiac circuit from elasticity to flaccidity.

SUMMARY AND CONCLUSIONS

An analysis of the relationship between the mean circulation time through the pulmonary circuit and the rate of the blood flow permits tentative deductions concerning the elastic properties of the pulmonary vasculature.

It is concluded that at resting flow rates of blood flow in normal individuals the pulmonary vasculature behaves as a simple elastic system. At high flow rate the the pulmonary vasculature behaves more nearly like a rigid system, while at very low flow rates the data suggest overstretching of the walls of the heart.

A more direct approach to this problem will be possible when it becomes feasible to make rapid serial measurements of the pulmonary blood flow.

REFERENCES

1. Doyle, J. T., Wilson, J. S., Lepine, C., and Warren, J. V.: An Evaluation of the Measurement of the Cardiac Output and of the So-Called Pulmonary Blood Volume by the Dye-Dilution Method, J. Lab. & Clin. Med. In press.
2. Doyle, J. T., Wilson, J. S., Estes, E. H., and Warren, J. V.: The Effect of Intravenous Infusions of Physiologic Saline Solution on the Pulmonary Arterial and Pulmonary Capillary Pressure in Man, J. Clin. Investigation **30**:345, 1951.
3. Unpublished observations.
4. Dexter, L., Dow, J. W., Haynes, F. W., Whittenberger, J. L., Ferris, B. G., Goodale, W. T., and Hellems, H. K.: Studies of the Pulmonary Circulation in Man at Rest. Normal Variations and the Interrelations Between Increased Pulmonary Blood Flow, Elevated Pulmonary Arterial Pressure and High Pulmonary "Capillary" Pressures, J. Clin. Investigation **29**:602, 1950.

BLOOD BILIRUBIN IN CONGESTIVE HEART FAILURE

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ALTHOUGH a rise in the blood bilirubin in congestive heart failure has long been a familiar phenomenon, relatively little attention has been paid to it. In the literature accessible to us we found only a limited number of articles dealing directly or indirectly with this subject.[1-15] No unanimity was reached as to the percentage of cases in which hyperbilirubinemia occurred and what type of bilirubin was involved in these cases. Much of this confusion is due to the use of older and less reliable methods for the determination of the bilirubin. Nevertheless, as early as 1913 Hijmans van den Bergh and Snapper[1] mentioned the occurrence of hyperbilirubinemia in cases of heart failure. They also noticed that this hyperbilirubinemia decreased as soon as the congestion disappeared. Generally a rise in the indirect bilirubin was noticed by most authors, and a so-called direct reaction only in a few serious cases with more pronounced obvious jaundice.

In recent years better methods for the determination of the bilirubin content of the blood have been developed, and it seemed worth while to study these relations with an improved method.

The method recently described by Schalm and Schulte[16] enables an estimation of the respective amounts of quick-reacting (direct) and slow-reacting (indirect) bilirubin simultaneously present in the blood. This is done by determining the speed of diazotation, expressed in the percentage of the total blood bilirubin that reacts with the azoreagent within ten minutes.

Using this method it was found that cases of congestive heart failure showed a rise in the total bilirubin content of the blood, with a distinctly higher percentage of diazotation within ten minutes. This was due to the existence of a mixture of quick-reacting (direct) and slow-reacting (indirect) bilirubin in the blood. The amount of indirect bilirubin exceeded that of direct bilirubin in most cases, this type of mixture being far more frequently found in cases of congestive heart failure than in the course of other lesions such as hepatitis or cholelithiasis with slight jaundice. Though this type of mixture is not absolutely diagnostic for congestive heart failure, it occurred so frequently in this condition that the laboratory staff, without any clinical knowledge of the patient, suggested the possibility of congestive heart failure on the grounds of this bilirubin determination alone.

Changes for better or for worse in the heart failure were reflected very accurately in the reaction of the bilirubin, which rose when the failure grew worse,

From the Municipal Hospital, Arnhem, Holland.
Received for publication June 27, 1952.

TABLE I. RHEUMATIC HEART DISEASE

CASE	DATE	TOTAL BILIRUBIN	10 MIN. (%)	DIRECT	INDIRECT	REMARKS
A. Congestive Heart Failure						
			Mitral Stenosis			
1.	26/10	7.20	48.6	2.58	4.62	Marked congestion
	3/11	2.26	42.0	0.62	1.64	
	12/11	1.82	46.7	0.61	1.21	
	28/11	1.36	13.2	—	1.36	
	6/12	1.57	17.8	—	1.50	Good recovery
2.	3/2	5.96	63.7	3.19	2.77	Congestion
	23/2	2.31	51.0	0.89	1.42	
	20/3	2.76	63.0	1.43	1.33	
	1/4	2.00	62.5	1.05	0.95	
	30/11	1.28	13.3	—	1.28	Recovered
3.	29/1	2.00	25.5	0.36	1.64	Congestion
	21/2	1.60	9.4	—	1.60	Recovered
4.	3/10	3.08	53.2	1.28	1.80	Marked congestion
	10/10	1.92	52.3	0.77	1.15	No complaints of cholelithiasis
	18/10	2.37	45.5	0.73	1.64	
	25/10	2.24	42.4	0.62	1.62	
	8/11	2.03	37.4	0.47	1.56	
	21/11	1.59	11.3	—	1.59	Recovered
			Second Hospitalization			
	25/4	7.1	64.8	3.98	3.12	Congestion with repeating attacks of cholelithiasis
	2/5	6.3	64.0	3.38	2.92	
	7/5	4.30	69.5	2.66	1.64	
	15/5	2.82	63.1	1.51	1.31	Operation
			Third Hospitalization			
	15/11	2.62	40.9	0.68	1.94	Congestion
	23/11	2.99	38.4	0.72	2.27	
	30/11	1.53	9.1	—	1.53	Recovered
5.	12/4	2.45	43.3	0.71	1.74	Congestion
	19/4	1.4	14.3	—	1.4	Recovered
B. No Congestive Heart Failure						
			Mitral Stenosis			
6.	2/10	1.59	10.7	—	1.59	Very slight congestion
	9/10	1.5	20.0	—	1.5	
	16/10	1.27	10.0	—	1.27	
	23/10	1.76	18.7	—	1.76	
7.	1/6	1.24	4.0	—	1.24	No congestion
	14/6	1.18	11.9	—	1.18	
		1.6	29.4	0.32	1.28	Pregnant, slight congestion
8.	15/11	1.13	7.1	—	1.13	No congestion
9.	5/8	0.95	8.4	—	0.95	No congestion
	3/11	1.15	4.4	—	1.15	
10.	9/6	1.57	15.9	—	1.57	No congestion

TABLE I. RHEUMATIC HEART DISEASE—(Cont'd)

CASE	DATE	TOTAL BILIRUBIN	10 MIN. (%)	DIRECT	INDIRECT	REMARKS
A. Congestive Heart Failure						
			Mitral Stenosis and Insufficiency			
11.	15/11	2.5	39.2	0.61	1.89	Congestion
	23/11	1.03	3.4	——	1.03	Recovered
			Mitral Insufficiency			
12.	4/7	3.26	34.3	0.72	2.54	Congestion
	21/7	1.06	7.5	——	1.06	Recovered
13.	11/5	3.73	40.0	0.93	2.8	Recurring congestion
	14/5	2.54	46.0	0.84	1.70	Autopsy cardiac cirrhosis
	29/5	5.44	41.6	1.55	3.89	
	23/6	4.31	64.1	2.35	1.96	
			Aortic Insufficiency			
14.	29/10	5.36	46.6	1.78	3.58	Congestion
			Aortic Insufficiency and Stenosis			
15.	14/8	1.87	16.0	——	1.87	No congestion
	13/10	3.29	60.2	1.61	1.68	Congestion

and fell when the clinical situation improved, to such extent that when the patient was compensated again the bilirubin content of the blood serum also returned to normal, with a normal speed of diazotation. When the improvement was only partial there was an initial fall in the bilirubin content, which then remained relatively stable but above the normal level. If there were permanent alterations in the liver parenchyma, seen predominantly in long-standing cases with recurring attacks of congestive heart failure, the bilirubin level never returned to normal and the diazotation speed remained elevated. This was unlike cases of acute heart failure without permanent liver damage, in which the bilirubin always returned to normal in both total content and diazotation speed.

The elevation of the bilirubin content seemed to be irrespective of the cause of heart failure.

The following observations were made of seventy-four cases.

RHEUMATIC HEART DISEASE

Mitral Stenosis.—In five cases of heart failure a rise in the total bilirubin content and the speed of diazotation was found, the amount of indirect bilirubin as a rule exceeding the amount of direct bilirubin. All patients made a good recovery, which was reflected in the return to normal of the total bilirubin and its diazotation speed (normal up to 1.5 to 2.0 units, with a percentage of 2 to 10 within ten minutes). In one patient these phenomena repeated themselves in two successive attacks of congestive heart failure (Case 4). A total bilirubin, falling within the "normal" range (2 units) but with a far too high speed of diazotation (62.5 per cent) indicated that a person had in reality a lower normal

bilirubin (1.28 units) to which, however, a certain amount of pathologic direct bilirubin was added (Case 2, date 1/4 and date 30/11). Five cases not suffering from heart failure showed normal values for total content and diazotation percentage within ten minutes.

Mitral Stenosis and Insufficiency.—The same reactions could be found in three congestive patients, in two of whom a recovery could be observed, whereas three noncongestive patients showed normal values.

Mitral Insufficiency.—Similar reactions were found in four patients with congestive heart failure. In one of them there was a recurring congestive failure, reflected in further rise or fall of bilirubin content. Even in the better period the total bilirubin content remained high, with a distinctly raised diazotation percentage within ten minutes. At autopsy the suspected cardiac cirrhosis was found (Case 13).

One noncongestive patient had normal values. These phenomena, which may be described as typical, were also found in *aortic insufficiency* (one congestive and one compensated case), *aortic stenosis* (one noncongestive case), and *aortic insufficiency and stenosis* (one congestive and one compensated case).

TABLE II. SYPHILITIC HEART DISEASE

CASE	DATE	TOTAL BILIRUBIN	10 MIN (%)	DIRECT	INDIRECT	REMARKS
			Aortic Insufficiency			
1.	12/12	2.10	37.5	0.50	1.60	Congestion
	25/1	1.00	5.0	——	1.00	Recovered
			HYPERTENSIVE HEART DISEASE			
2.	8/3	2.62	58.6	1.26	1.36	Marked congestion
	24/3	1.92	31.2	0.40	1.52	
	29/9	1.24	6.5	——	1.24	Recovered
3.	10/3	3.75	67.7	2.23	1.52	Marked congestion
	29/3	2.72	58.8	1.32	1.40	
	17/5	1.75	48.6	0.62	1.13	Partially recovered
4.	8/5	5.33	58.0	2.59	2.74	Marked congestion
	30/5	2.04	46.6	0.67	1.37	Partially recovered
			Second Hospitalization			
	24/11	6.50	64.6	3.62	2.88	Died. Autopsy: pronounced engorgement of the liver with beginning cirrhosis
	6/12	5.80	66.0	3.34	2.46	

SYPHILITIC HEART DISEASE

Aortic Insufficiency.—Two congestive cases, one of which recovered, and four noncongestive cases were observed with similar conclusions.

TABLE III

CASE	DATE	TOTAL BILIRUBIN	10 MIN (%)	DIRECT	INDIRECT	REMARKS
			CORONARY ARTERY DISEASE			
			Chronic			
1.	16/4	2.09	21.5	0.33	1.76	Auricular fibrillation.
	8/5	1.06	4.7	——	1.06	Recovered
2.	19/2	2.50	34.0	0.55	1.95	Marked congestion
	26/2	1.09	5.5	——	1.09	Recovered
3.	26/2	2.94	42.0	0.81	2.13	Congestion
	7/10	1.3	13.0	——	1.3	Recovered
			Acute Coronary Thrombosis			
	Blood Sampling After Attack					
1.	1 day	1.68	8.5	——	1.68	E.C.G. typical. Lateral infarct. Died after 5 days
2.	1 day	1.24	3.2	——	1.24	E.C.G. typical. Anterior infarct. Died after 2 days
3.	1 day	1.1	12.7	——	1.1	Died after 7 days. Obduction: ant. coronary thrombosis
4.	6 days	1.92	7.0	——	1.92	E.C.G. typical. Anterior infarct. Recovered
5.	3 days	1.9	9.5	——	1.9	E.C.G. typical.
	4 days later	1.57	54.1	0.69	0.88	Anterior infarct. Recovered
	4 days later	1.24	24.2	0.21	1.03	
	7 days later	1.12	22.3	0.18	0.94	
	9 days later	1.03	4.8	——	1.03	
6.	3 days	2.52	36.5	0.58	1.94	E.C.G. typical. Anterior infarct. Recovered
	3 days later	1.82	30.0	0.36	1.46	
	4 days later	0.9	6.7	——	0.9	
			MISCELLANEOUS			
1.	6/2	2.32	43.0	0.70	1.62	Cor pulmonale
	10/2	1.03	8.7	——	1.03	Congestion
	1/3	0.60	6.6	——	0.60	Recovered
2.	14/10	3.20	48.4	1.14	2.06	Constrictive pericarditis.
	27/10	2.84	52.8	1.15	1.69	Congestion

HYPERTENSIVE HEART DISEASE

Eight congestive cases were observed in this series. Four of them recovered and showed a typical normalization of the bilirubin. Three recovered only partly, this being reflected in a fall in the total bilirubin, with a quicker fall in the direct component of the bilirubin and a slower decrease of the slow bilirubin (Cases 2 and 3). Case 4 showed this twice before dying. The pathologic composition of the bilirubin which remained even after clinical improvement suggested a permanent damage to the liver parenchyma, which was proved to be the case at autopsy. Of the three noncongestive cases two showed normal values. One had a total above normal with a relatively low diazotation percentage within ten minutes, probably due to a slight general impairment of the liver parenchyma, (due to former attacks of congestive failure) in converting indirect or direct bilirubin.

CORONARY ARTERY DISEASE

Chronic.—Nineteen congestive cases of this category were studied. Eight of them made a good recovery, with the typical bilirubin findings. Some of these cases did not quite attain a normal diazotation percentage within ten minutes. This was undoubtedly due to a slight and permanent hepatic damage in these conditions of long standing, in which the period of investigation formed merely a short interlude. The remaining cases with partial or no recovery all maintained an increased diazotation percentage within ten minutes and/or increased total bilirubin. Four noncongestive cases showed normal values.

Acute Coronary Thrombosis.—Within one day after the attack no increase in the speed of diazotation and total bilirubin was found in three cases of the six studied. One other case showed normal values six days after the acute attack.

Especially instructive, however, were the findings in Cases 5 and 6. Immediately after the attack no changes in the bilirubin were found. Some days later, however, the total bilirubin and especially the diazotation percentage within ten minutes showed a definite rise. This was interpreted as the result of congestive failure and both values returned to normal as the clinical situation improved and compensation was once more attained.

MISCELLANEOUS

In one case of cor pulmonale, recovery from congestive heart failure was reflected in the return to normal of the bilirubin values. One case of constrictive pericarditis with congestive heart failure of sixteen years' standing maintained the same pathologic values throughout the observation.

DISCUSSION

In congestive cardiac failure, irrespective of its cause, a rise in the blood bilirubin was found. This confirmed the findings of a number of earlier investigators. There is no unanimity as to the cause of this hyperbilirubinemia. Hijmans van den Bergh simply named congestion as the cause. Eppinger[17] thought that

blood in infarctions of the lung might be the cause of an increased production of bilirubin, which, combined with impaired function of the liver, might result in retention of bilirubin in the blood. This view was shared by some others. We would stress that only an increase of indirect bilirubin in the blood could be thus explained, but not the presence of direct bilirubin. Yet this last type of bilirubin was found in a few cases in former times and is indeed regularly found when the bilirubin is determined by modern methods. Resnik and Keefer,[18] Rich and Resnik,[19-20] on the other hand, indicated anoxia, damaging the function of the liver, being the principal cause of hyperbilirubinemia, which view was supported by recent experiments of Myers and Hickam.[21] By means of catheterization of the right heart and hepatic veins the latter found a marked unsaturation of the hepatic venous blood in cardiac failure. They considered this relative anoxia as a cause of the central necrosis of the liver lobule. Recently Sherlock[15] demonstrated that centrilobular hepatic necrosis occurred almost invariably in these cases. With increasing heart failure this necrosis became more widespread, disappearing when the cardiac congestion responded to treatment. In our opinion this regularly occurring central necrosis explains why in all cases of congestive heart failure a certain amount of direct bilirubin could be found together with an increased amount of indirect bilirubin. Furthermore, Myers and Hickam found that the hepatic blood flow was diminished in congestive failure, and was unrelated to the pressure in the right auricle, which, according to Sherlock, tends to be very high in patients with severe jaundice due to cardiac congestion.

The type of bilirubin found in these cases has often been a matter of controversy. In the old phraseology the reaction was often "biphasic," becoming "direct" in cases with more pronounced jaundice. As already suggested by Hijmans van der Bergh and Hartog,[22] modern methods have proved that in cases of biphasic reaction, as it was formerly called, there was a mixture of quick-reacting (direct) and slow-reacting (indirect) bilirubin simultaneously present in the blood in amounts that did not differ greatly from one another. The amount of slow bilirubin as a rule predominated.

Only when the amount of direct bilirubin greatly exceeded the amount of indirect bilirubin did the reaction become "direct" in the old phraseology.

The total bilirubin, determined with the reaction of Schalm and Schulte, in congestive heart failure, is composed of an increased amount of indirect bilirubin (always present in the blood in normal quantities), with an additional amount, generally smaller, of direct bilirubin. Upon clinical improvement these amounts both decrease, the direct component disappearing first, leaving a moderately increased indirect component that returns to normal in the course of further clinical improvement. These schematisized reactions were found in cases of acute congestive heart failure followed by a more or less complete recovery. In cases of long standing and especially with repeated attacks of congestive heart failure, the total amount of bilirubin, though decreasing upon partial improvement, remained at too high a level with an increased speed of diazotation owing to permanent damage to the liver parenchyma.

These reactions can be explained as follows: The cells of the liver parenchyma are slightly damaged functionally in congestive heart failure. The direct cause

TABLE IV

DATE	TOTAL BILIRUBIN CONTENT OF BLOOD	10 MIN. (%)	BILIRUBIN		THYMOL TURBIDITY (UNITS)	GROSS REACTION	BROMSULPHALEIN TEST (%)	UROBILIN IN URINE
			DIRECT	INDIRECT				
Mitral Stenosis With Congestive Failure (see Table I, Case 4)								
3–10	3.08	53.2	1.28	1.80	7.1	1.26	23	+++
10–10	1.92	52.3	0.77	1.15	9.1	1.44	20	+++
18–10	2.37	45.5	0.73	1.64	7.1	1.31	28	+++
25–10	2.24	42.4	0.62	1.62	6.3	1.43	18	++
8–11	2.03	37.4	0.47	1.56	5.1	1.40	13	++
21–11	1.59	11.3	—	1.59	6.0	1.46	9	–
Hypertensive Heart Disease With Congestive Failure (see Table II, Case 4)								
8–5	5.53	58.0	2.59	2.74	6.9	1.26	—	+++
16–5	3.73	49.8	1.38	2.35	5.0	1.30	25	+++
23–5	2.74	52.5	1.06	1.68	14.0	1.23	43	+++
30–5	2.04	46.6	0.67	1.37	7.2	1.37	20	+++

of this is not clear, but might be relative anoxia. The conversion of the normal indirect bilirubin of the blood into direct bilirubin is thus hampered, and a certain retention of indirect bilirubin takes place. Whether this conversion takes place within Küpffer's cells or within the liver cells themselves is not important in this question. The part of the indirect bilirubin converted into direct bilirubin is excreted, but can partly leak back into the blood because of the anatomic damage to the liver parenchyma. Sherlock recently showed that such anatomic damage is regularly to be found in livers of decompensated patients, being foci of necrosis, which lesions disappear with the cessation of the circulatory insufficiency. The direct bilirubin then disappears from the blood, leaving the indirect bilirubin still above normal owing to the continuing disturbance of the finer function of the liver parenchyma. This amount of indirect bilirubin is completely normal when clinical recovery is completed. In those cases in which functional and anatomic damage is permanent, the total bilirubin content and its percentage of diazotation are not normal, though often decreasing upon partial recovery. In this way an acceptable explanation of the facts can be given, fitting in well with the other clinical and anatomic findings. As to the theory that the hyperbilirubinemia might be due to the destruction of extravasated red blood cells in the infarcts, we have already mentioned that if this were the sole cause, the occurrence of direct bilirubin in the blood could not be explained. Besides, none of our patients showed the clinical syndrome of pulmonary infarction. This was also emphasized by Heilbrun and Hubbard[11] in cases controlled by autopsy.

In our experience the total bilirubin of the blood with its percentage of diazotation within ten minutes reflects very accurately the degree of congestive

TABLE IV—(Cont'd)

ARTERIAL OXYGEN SATURATION (VOL. %)	CIRCULATION TIME (ARM-TONGUE) (SEC.)	VENOUS PRESSURE (mm. H_2O)	VITAL CAPACITY (C.C.)	EDEMA	ASCITES	CYANOSIS	DYSPNEA	ENGORGEMENT OF LIVER	REMARKS
	31	75		+	−	+	−	1	
93	18.5	85	2100	−	−	Slight	−	−	17-10 Sore
97	9	−		−	−	Slight	−	−	throat with
	35	70	2600	−	−	−	−	−	fever
	25	80	2500	−	−	−	−	2	
	16	−		−	−	−	−	−	
91	42	182	1500	+	−	+	+	+	
−	37	85		+	−	+	+	+	
−	30	67		Slight	−	+	−	+	
−	30	50		Slight	−	+	−	+	

heart failure and the possible existence of permanent hepatic damage. Though the purpose of this article is merely to draw attention to the bilirubin relations in heart failure, we determined in a number of cases the sensitivity of this phenomenon compared with determinations of other phenomena, for example, venous pressure, circulation time, vital capacity, arterial oxygen saturation, and liver function tests. As far as our experience extends, at the present, the total bilirubin elevation with increased diazotation speed proved itself to be a very sensitive and quantitatively reliable phenomenon.

SUMMARY

It has been shown that in congestive heart failure the bilirubin content of the blood is raised. Determination of the percentage of diazotation of this bilirubin within ten minutes by the method described by Schalm and Schulte indicates that in these cases a mixture of quick-reacting (direct) bilirubin and slow-reacting (indirect) bilirubin exists in the blood, the amount of slow-reacting bilirubin being as a rule the larger one. The reaction of the bilirubin corresponds closely to the degree of congestive failure. When this returns to normal, the bilirubin of the blood returns to normal also. When compensation has been attained and the total bilirubin and speed of diazotation nevertheless remain above normal, permanent hepatic damage is present.

REFERENCES

1. Hijmans van den Bergh, A. A., and Snapper, I.: Die Farbstoffe des Blutserums, Deutsches Arch. f. klin. Med. **110**:540, 1913.
2. Hijmans van den Bergh, A. A., and Muller, P.: Ueber eine direkte und indirekte Diazoreaktion auf Bilirubin, Biochem. Ztschr. **77**:90, 1916.

3. Fishberg, A. M.: Jaundice in Myocardial Insufficiency, J. A. M. A. **80**:1516, 1923.
4. Keefer, C. S., and Resnik, W. H.: Jaundice Following Pulmonary Infarction in Patients With Myocardial Insufficiency. A Clinical Study, J. Clin. Investigation **2**:375, 1926.
5. Meakins, J.: Distribution of Jaundice in Circulatory Failure, J. Clin. Investigation **4**:135, 1927.
6. Joliffe, N.: Liver Function Tests in Congestive Heart Failure, J. Clin. Investigation **8**:419, 1930.
7. Ernstene, C.: Jaundice in Heart Disease, M. Clin. North America **15**:1005, 1931.
8. Robertson, W. E., Swalm, W. A., and Konzelmann, F. W.: Functional Capacity of the Liver, Comparative Merits of Five Most Popular Tests, J. A. M. A. **99**:2071, 1932.
9. Kugel, M. A., and Lichtmann, S. S.: Factors Causing Clinical Jaundice in Heart Disease, Arch. Int. Med. **52**:16, 1933.
10. Routier, D., Cottet, J., and Molinghen, P.: Contribution à l'étude des fonctions hépatiques au cours de l'asystolie, Arch. d. mal. de l'app. digestif. **25**:801, 1935.
11. Heilbrun, N., and Hubbard, R. S.: The Measurement of the Chloroform-soluble Fraction of Bilirubin in Persons With Jaundice and Its Significance, J. Lab. & Clin. Med. **26**:576, 1940.
12. Chavez, I., Sepulveda, B., and Ortega, A.: The Functional Value of the Liver in Heart Disease, J. A. M. A. **121**:1276, 1943.
13. Felder, L., Mund, A., and Parker, J. G.: Liver Function Tests in Chronic Congestive Heart Failure, Circulation **2**:286, 1950.
14. White, F. J., Wallace, R. B., Gnasse, A. M., Kamp, N. F., Prive, H. P., and Leevy, C. M.: Hepatic Abnormalities in Congestive Heart Failure, Circulation **3**:501, 1951.
15. Sherlock, S.: The Liver in Heart Failure, Brit. Heart J. **13**:273, 1951 (reference in J. A. M. A. **147**:903, 1951).
16. Schalm, L., and Schulte, M. J.: The Quantitative Determination of the Two Types of Bilirubin Simultaneously Present in the Blood, and Its Clinical Importance, Am. J. M. Sc. **219**:606, 1950.
17. Eppinger, H.: Die Leberkrankheiten, Wien, 1937, Julius Springer.
18. Resnik, W. H., and Keefer, C. S.: Jaundice Following Pulmonary Infarction in Patients With Myocardial Insufficiency. An Experimental Study, J. Clin. Investigation **2**:389, 1926.
19. Rich, A. R., and Resnik, W. H.: On the Mechanism of the Jaundice Following Pulmonary Infarction in Patients With Heart Failure, Bull. Johns Hopkins Hosp. **38**:75, 1926.
20. Rich, A. R.: The Pathogenesis of the Forms of Jaundice, Bull. Johns Hopkins Hosp. **47**:338, 1930.
21. Myers, J. D., and Hickam, J. B.: An Estimation of the Hepatic Blood Flow and Splanchnic Oxygen Consumption in Heart Failure, J. Clin. Investigation **27**:620, 1948.
22. Hijmans van den Bergh, A. A., and Hartog, H. A. Ph.: Mesure de la vitesse de réaction de la bilirubine directe et indirecte, Bull. Acad. de méd. de Roumanie, first year, II, No. 4.

CONGENITAL HEART DISEASE: AN ANALYSIS OF ELECTROCARDIOGRAPHIC PATTERNS IN FORTY-FOUR PATIENTS WITH ELEVATED RIGHT VENTRICULAR PRESSURE

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MYERS and associates[1] have recently analyzed the electrocardiogram in autopsy-proved right ventricular hypertrophy of varying etiology. Johnson and associates[2] have analyzed the electrocardiographic findings in right ventricular hypertrophy due to chronic pulmonary disease and have correlated the results with mean right pulmonary artery pressures. The present study represents an analysis of electrocardiographic findings in congenital heart disease, using elevated right ventricular pressure and/or increased right ventricular flow (and thus increased right ventricular work) as a measure of right ventricular hypertrophy.

MATERIAL AND METHODS

The material was gathered from a series of 100 patients studied by cardiac catheterization according to the techniques of Cournand and associates.[3] Our own modifications of this technique have been previously described.[4,5] We chose for this study all patients who had congenital heart disease and a right ventricular systolic pressure of 30 mm. Hg or above. We considered this pressure level to be just beyond the upper limit for the normal right ventricle.[6] The material consisted largely of patients with isolated right ventricular hypertrophy. A smaller group with involvement of both left and right ventricles necessarily fell within the scope of this study (for example, patent ductus arteriosus, ventricular septal defects, etc.). This group was included in order to give a comprehensive picture of the electrocardiogram in the presence of elevated right ventricular pressure.

The data consisted of: (1) right ventricular systolic and diastolic pressures as determined by strain gauge manometer, and right ventricular mean systolic ejection pressures as measured by planimetric integration, (Gorlin and Gorlin[7]); (2) electrocardiographic data as follows: the amplitude of Q, R, S, R′, and T in V_1, V_2, V_5, V_6, aV_R, and V_{3R}, the width of precordial QRS, the initial appearance of Q over the left side of the heart, and the R/S ratios in V_{3R}, V_1, V_5, and V_6. In addition, the preintrinsicoid deflections from the onset

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Received for publication March 17, 1952.

of QRS to the peak of R were measured in V_{3R}, V_1, V_5, and V_6. Right ventricular output was calculated according to the usual Fick equation. In the tables, it is recorded as liters per minute without correction to cardiac index. In patients with shunts, the formulas of Cournand and associates[3] were employed to calculate output; for example, in tetralogy of Fallot, right ventricular output equals the sum of pulmonary flow and the flow through the right-left shunt of the overriding aorta. Right ventricular work was obtained using the formula of Gorlin and associates[8]:

$$W_R = \frac{(CI \times 1.055)\ ([PA_m - RA_m] \times 13.6)}{1000} \text{ kg.M. per minute per sq.M.}$$

but using right ventricular mean systolic ejection pressure in place of mean pulmonary artery pressure. Right ventricular work greater than 1 kg.M./min./sq.M. was considered abnormal. The right ventricular flows, as recorded in the tables, were corrected per square meter of body surface in employing the formulas of Gorlin.

DATA

The forty-four electrocardiograms have been divided into three groups:

Group I.—Electrocardiographic pattern of right ventricular hypertrophy. (Fig. 1.) This group of eighteen cases (Table I) show tall R over the right ventricle, usually tallest in V_1. The R/S ratio over the right ventricle was greater than one, and there was a relatively small R and deep S in V_5 and V_6. A relatively late preintrinsicoid deflection was found over the right ventricle and a relatively early preintrinsicoid deflection over the left ventricle. The QRS complex was occasionally slurred, but actual notching did not appear. The duration of QRS was less than 0.09 second.

Group II.—"Incomplete right bundle branch block." (Figs. 2 and 3.) This group of seventeen cases (Table II) was classified as incomplete right bundle branch block and showed an RSR′ pattern in V_1 and/or V_{5R}. The QRS complex was greater than 0.08 second and less than 0.11 second. The preintrinsicoid deflection measured to the peak of R′ was prolonged over the right ventricle.

Two main variants were present. In Group II A (Fig. 2) the R and R′ waves of Lead V_1 and/or Lead V_{3R} were both small; R′ was almost always the taller. The R′ deflection did not exceed 6 mm. in height. In Group II B (Fig. 3) the R′ deflection of V_1 and/or V_{3R} was tall, being at least 7 mm. and usually more than 10 mm. in height.

Group III.—Normal or "balanced" electrocardiogram. (Fig. 4.) This group of nine cases (Table III) differed radically from the others. The patients showed anatomic left ventricular as well as right ventricular hypertrophy. The electrocardiograms in general suggested this bilateral ventricular hypertrophy by showing no significant reversal of the R/S ratio in V_1. The preintrinsicoid deflection was in general later than normal, but not later than the preintrinsicoid deflection in V_6.

TABLE I.

NAME	AGE (YRS.)	DIAGNOSIS*	RIGHT VENTRICULAR MEAN SYSTOLIC EJECTION PRESSURE (Mm. Hg)	V_{3R}		V_1		V_6		R/S RATIO			PREINTRINSICOID DEFLECTION TIME (SEC.)			WIDEST QRS (SEC.)	RIGHT VENTRICULAR FLOW (L./min.)	RIGHT VENTRICULAR WORK (Kg.M./min./sq.M.)
				R	S	R	S	R	S	V_{3R}	V_1	V_6	V_{4R}	V_1	V_6			
1. C. R.	27	Fallot[1]	60	36.0	1	38.0	1	3.5	20.0	36.0	38.0	0.18	0.052	0.049	0.014	0.080	5.2	2.77
2. V. A.	29	Eisen.[2]	75	—	—	10.5	1	11.0	12.0	—	10.5	0.92	—	0.040	0.026	0.090	6.8	4.92
3. D. M.	7	Fallot[1]	85	35.0	14	37.0	18	4.0	14.0	2.5	2.06	0.29	0.016	0.045	0.024	0.060	6.5	11.92
4. D. M.	4	Dext.[3] & Fallot[1]	57	6.0	12	14.0	25	3.0	13.0	0.5	0.56	0.25	0.030	0.030	0.015	0.080	2.7	2.99
5. M. R.	7	T.P.V.[4]	114	11.0	4	11.5	10	1.0	10.0	2.75	1.15	0.10	0.040	0.036	Inf.†	0.090	7.0	11.01
6. J. Q.	21	Fallot[1]	69	12.5	1	10.5	1	4.0	1.0	12.5	10.5	4.00	0.044	0.035	0.022	0.075	5.4	2.61
7. P. M.	18	Unknown	63	5.0	1	6.5	1	26.0	25.0	5.0	6.5	1.04	0.031	0.024	0.020	0.070	2.7	3.86
8. F. Z.	25	P.S.[5]	97	—	—	15.0	1	3.0	6.0	—	15.0	0.5	—	0.036	0.023	0.070	1.9	1.43
9. S. D.	20	Fallot[1]	102	11.0	1	12.0	1	6.0	8.0	11.0	12.0	0.75	0.039	0.043	0.020	0.075	4.6	3.99
10. R. G.	26	A.S.D.[6]	75	11.0	3	15.5	7	8.5	12.0	3.66	2.21	0.71	0.022	0.032	0.010	0.065	10.8	8.27
11. G. M.	27	A.S.D.[6]	59	—	—	28.5	2	35.0	16.5	—	14.2	2.12	—	0.047	0.020	0.090	5.8	2.63
12. R. W.	6	V.S.D.[7] & P.S.[5]	135	30.0	1	38.0	1	1.0	18.0	30.0	38.0	0.06	0.034	0.049	0.020	0.070	2.3	5.22
13. P. D.	18	A.S.D.[6]	65	24.0	1	25.0	1	18.0	14.0	24.0	25.0	1.29	0.034	0.034	0.029	0.080	6.9	3.96
14. G. A.	17	A.S.D.[6] & P.S.[5]	115	14.0	1	15.5	1	1.0	7.0	14.0	15.5	0.14	0.030	0.021	0.016	0.070	2.3	2.45
15. G. L.	9	A.S.D.[6]	42	3.0	2	4.0	1	10.0	6.0	1.5	4.0	1.66	0.028	0.035	0.017	0.080	3.9	1.78
16. S. K.	23	Eisen.[2]	65	—	—	8.0	1	7.0	9.0	—	8.0	0.78	—	0.040	0.018	0.090	7.6	3.98
17. B. T.	21	High V.S.D.[7]	41	—	—	6.5	1	24.0	11.5	—	6.5	2.09	—	0.042	0.024	0.080	7.5	3.19
18. G. H.	4	Eisen.[2]	90	13.0	5	21.0	5	13.0	6.0	2.6	4.25	2.17	0.040	0.042	0.020	0.075	5.4	10.33

*Diagnosis:
[1]Tetralogy of Fallot
[2]Tetralogy of Eisenmenger
[3]Dextrocardia
[4]Transposed pulmonary veins
[5]Pulmonary stenosis
[6]Auricular septal defect
[7]Ventricular septal defect
†Infinity.

TABLE II

NAME	AGE (YRS.)	DIAGNOSIS*	RIGHT VENTRICULAR MEAN SYSTOLIC EJECTION PRESSURE (Mm. Hg)	V_{3R}		V_1		V_6		R/S RATIO			PREINTRINSICOID DEFLECTION TIME (SEC.)			WIDEST QRS (SEC.)	RIGHT VENTRICULAR FLOW (L./min.)	RIGHT VENTRICULAR WORK (Kg.M./min./sq.M.)
				R′	S′	R′	S′	R	S	V_{3R}	V_1	V_6	V_{3R}	V_1	V_6			
Group II A																		
1. P. C.	39	A.S.D.[1] & P.S.[2]	95	3.0	3.0	3.0	6.0	6	1.0	1.00	0.05	6.00	0.035	0.049	0.037	0.090	3.5	2.58
2. C. S.	46	A.S.D.[1]	30	5.0	1.0	5.0	5.0	12	2.0	5.00	10.00	6.00	0.060	0.061	0.025	0.080	9.4	2.22
3. B. P.	13	T.P.V.[3]	24	2.0	1.0	4.0	1.0	5	3.5	2.00	4.00	1.43	0.049	0.040	0.025	0.070	6.8	1.60
4. F. E.	42	T.P.V.[3]	27	3.0	1.0	3.0	1.0	11	4.0	3.00	3.00	2.75	0.055	0.058	0.024	0.100	16.9	4.03
5. W. H.	28	High & V.S.D.[4]	63	5.5	8.0	6.0	13.0	23	2.0	0.68	0.46	11.50	0.055	0.050	0.050	0.090	14.5	6.79
6. R. L.	26	V.S.D.[4] & P.S.[2]	39	4.0	3.0	2.0	4.0	20	2.0	1.33	0.50	10.00	0.040	0.043	0.020	0.085	7.1	2.69
7. L. B.	21	Fallot[5]	120	4.0	1.0	0.5	6.0	6	1.0	4.00	0.08	6.00	0.055	Inf.†	0.032	0.075	2.5	2.94
8. R. H.	38	A.S.D.[1]	60	3.0	2.5	2.0	3.0	6	13.0	1.20	0.66	0.46	0.062	0.064	0.049	0.100	3.4	1.73
9. B. R.	6	A.S.D.[1]	39	3.0	1.0	2.5	1.0	30	19.0	3.00	2.50	1.58	0.050	0.055	0.040	0.080	9.2	6.51

Group II B

10. R. S.	37	A.S.D.[1]	90	5.0	1.0	7.0	1.0	4	11.0	5.00	7.00	0.36	0.084	0.088	0.018	0.120	8.9	7.46
11. E. K.	17	A.S.D.[1]	33	16.0	2.5	9.0	1.0	41	7.0	6.40	9.00	5.90	0.082	Inf.†	0.060	0.100	17.1	4.33
12. R. R.	14	P.S.[2]	93	16.0	1.0	20.0	1.0	8	7.0	16.00	20.00	1.14	0.050	0.046	0.031	0.100	6.4	5.47
13. P. M.	10	A.S.D.[1]	21	11.0	1.0	14.0	1.0	13	4.0	11.00	14.00	3.25	0.064	0.059	0.033	0.090	11.1	2.91
14. D. F.	43	Eisen.[6]	123	11.5	1.0	17.0	1.0	10	11.5	11.50	17.00	0.87	0.042	0.059	0.018	0.090	6.6	7.20
15. S. H.	4	T.P.V.[3]	63	15.0	1.0	18.0	1.0	15	30.0	15.00	18.00	0.50	0.054	0.069	0.026	0.070	3.2	3.91
16. G. G.	12	P.S.[2]	33	6.0	2.0	12.0	2.0	8	12.0	3.00	6.00	0.66	0.039	0.042	0.018	0.080	4.2	1.62
17. B. H.	23	A.S.D.[1] & P.S.[2]	61	—	—	11.0	0.5	1	23.0	—	24.00	0.04	—	0.060	0.020	0.080	5.8	3.16

*Diagnosis:
[1]Auricular septal defect
[2]Pulmonary stenosis
[3]Transposed pulmonary veins
[4]Ventricular septal defect
[5]Tetralogy of Fallot
[6]Tetralogy of Eisenmenger
†Infinity.

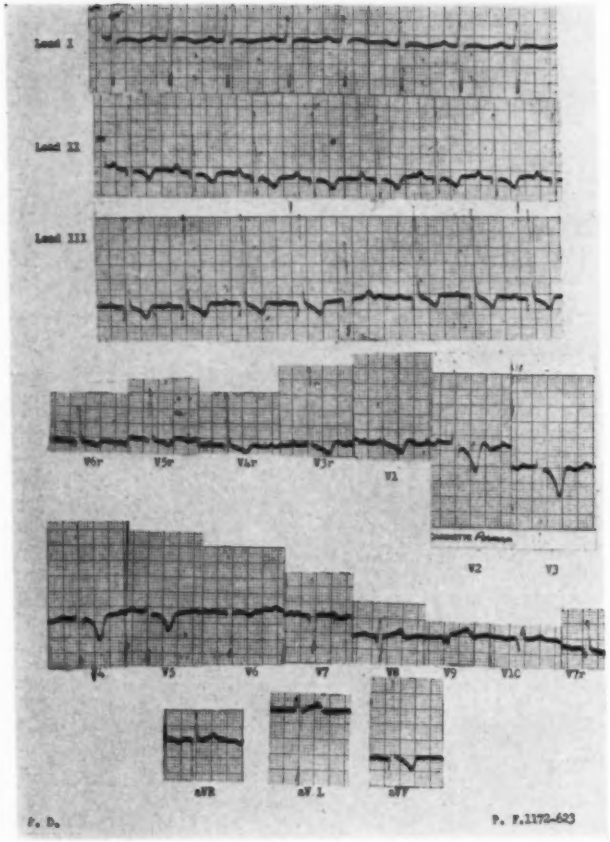

Fig. 1.

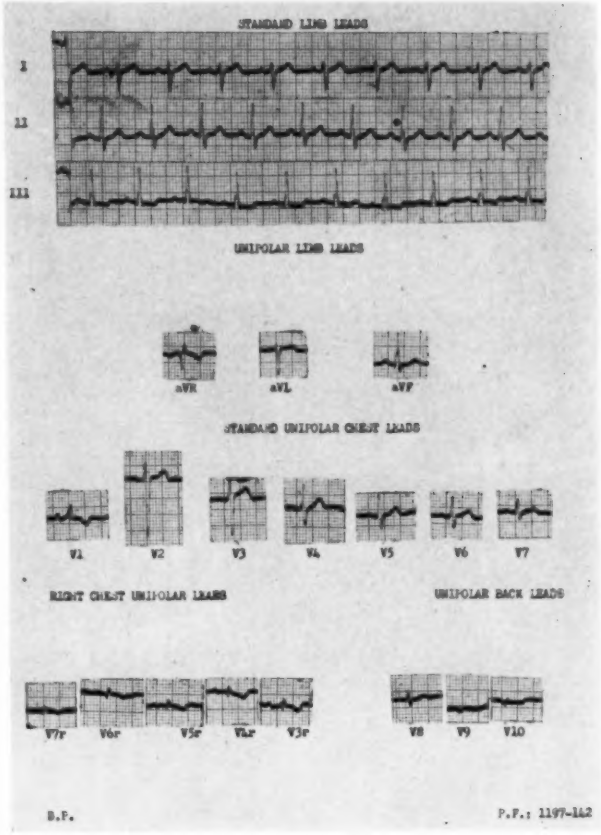

Fig. 2.

Fig. 1.—Example of Group I tracing: "pure" right ventricular hypertrophy.

Fig. 2.—Example of Group II A tracing: partial right bundle branch block with R′ (prime).

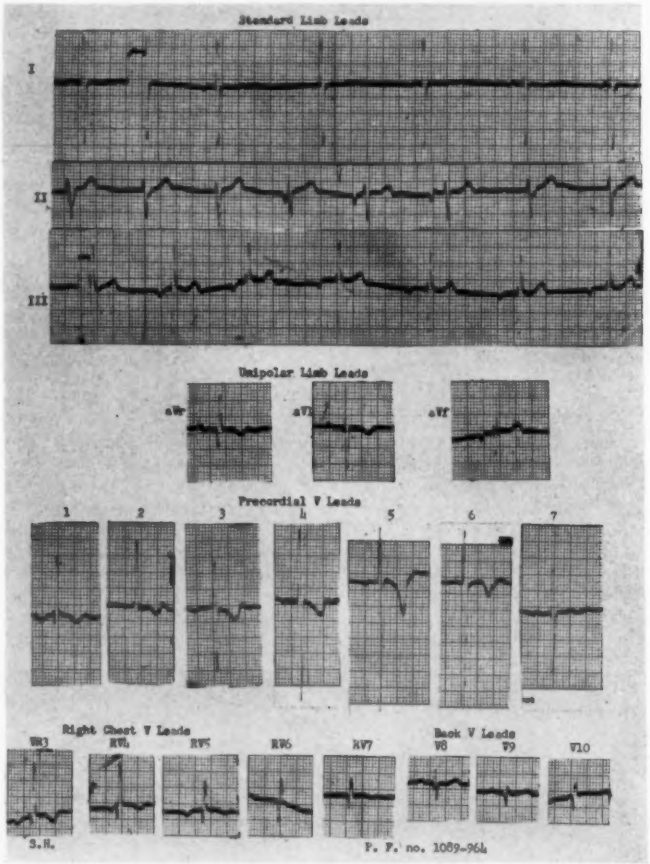

Fig. 3.

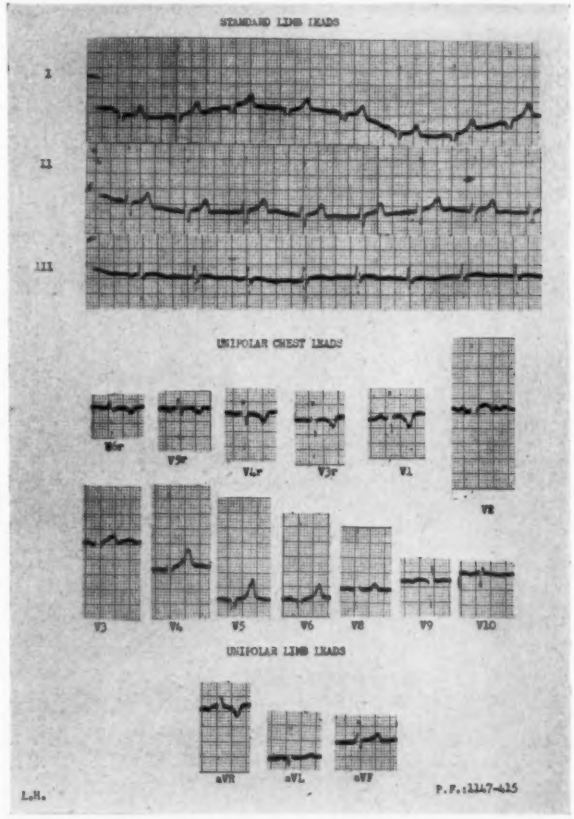

Fig. 4.

Fig. 3.—Example of Group II B tracing: partial right bundle branch block with tall R′.

Fig. 4.—Example of Group III electrocardiogram: "balanced" hypertrophy.

TABLE III

NAME	AGE (YRS.)	DIAGNOSIS*	RIGHT VENTRICULAR MEAN SYSTOLIC EJECTION PRESSURE (Mm. Hg)	V_{3R}		V_1		V_6		R/S RATIO			PREINTRINSICOID DEFLECTION TIME (SEC.)			WIDEST QRS (SEC.)	RIGHT VENTRICULAR FLOW (L./min.)	RIGHT VENTRICULAR WORK (Kg.M./min./sq.M.)
				R	S	R	S	R	S	V_{3R}	V_1	V_6	V_{3R}	V_1	V_6			
1. D. H.	2	P.D.A.[1]	33	12.0	18	15.0	29	34	1.0	0.67	0.52	34.0	0.025	0.014	0.033	0.060	4.8	3.91
2. V. K.	18	P.D.A.[1]	39	1.0	10	1.5	24	14	1.0	0.10	0.06	14.0	0.009	0.015	0.034	0.080	9.0	3.34
3. R. D.	23	V.S.D.[2]	35	0.5	1	0.25	5	5	5.5	0.50	0.05	0.91	Inf†.	0.012	0.030	0.090	6.6	2.01
4. L. H.	10	P.D.A.[1]	45	6.0	13	22.0	27	25	1.0	0.82	0.57	25.0	0.024	0.033	0.037	0.090	5.0	2.01
5. C. S.	4	V.S.D.[2]	33	2.0	11	1.5	9	25	1.0	0.18	0.16	25.0	0.013	0.043	0.032	0.065	5.1	3.93
6. M. G.	40	Coarc.[3]	33	0.5	13	0.5	18	9	8.0	0.04	0.03	1.13	0.012	0.017	0.026	0.100	4.6	1.16
7. L. M.	31	V.S.D.[2] & P.S.[4]	61	—	—	16.0	15	20	1.0	—	1.07	20.0	—	0.027	0.024	0.085	4.7	2.87
8. P. C.	8	V.S.D.[2]	30	17.0	16	17.0	16	29	1.5	1.08	1.08	19.3	0.020	0.021	0.029	0.065	4.0	1.65
9. G. H.	20	High V.S.D.[2]	87	4.0	3	8.5	8	17	7.0	2.33	1.06	2.43	0.032	0.042	0.042	0.085	9.1	5.88

*Diagnosis:
[1]Patent ductus arteriosus
[2]Ventricular septal defect
[3]Coarctation of the aorta
[4]Pulmonary stenosis
†Infinity

DISCUSSION

Group I.—This group followed the pattern of Myers' Group A[1]: ". . . (a) an abnormally large R in proportion to S in V_1 and a diminution in R/S ratio in leads from the left precordium, (b) a prolonged preintrinsicoid deflection in V_1 (generally between 0.03 and 0.05 seconds) and greater than that in V_5, V_6, (c) a tendency to a small Q in V_1, (d) a tendency to inversion of T in V_1, and an upright T in V_6, (e) total duration of QRS less than 0.12 seconds and generally within the normal range, and (f) absence of notching or double peaking of RV_1."

In all but two of our cases the preintrinsicoid deflection in V_1 was above the maximum normal limit of 0.23 second. In all patients the preintrinsicoid deflection over the right ventricle was more prolonged than over the left ventricle. A small Q in V_1 was present in five of our eighteen cases. In twelve patients the T wave was inverted in V_1. The chief feature in this group of congenital patients differing from the cases described by Myers and associates[1] and Johnson and associates[2] was in the exaggerated height of R over the right ventricle and the unusually large R/S ratios in V_1 and V_{3R}.

Group II.—The seventeen electrocardiograms in this group were interpreted as partial right bundle branch block. The chief feature of this pattern was an M-shaped complex over the right ventricle with a QRS duration of between 0.08 and 0.11 second. Myers and associates[1] has outlined the following criteria for partial right bundle branch block: ". . . (a) prominent R, coarsely notched or double peaked over the right side of the precordium, (b) intrinsicoid deflection time in V_1 generally between 0.05 and 0.075 second (exceeding that in uncomplicated right ventricular hypertrophy), (c) duration of QRS usually between 0.09 and 0.11 second, (d) absence of Q waves over the right side of the precordium."

The M-shaped QRS over the right side of the precordium may assume a variety of forms, well differentiated, and described by Barker and Valencia.[9] We have distinguished two main patterns in our series: (1) those electrocardiograms with a small R′, and (2) those with a tall R′. This arbitrary subdivision (adapted from Barker and Valencia[9]) was utilized to bring out differences in the R/S ratio in each category.

Group II A.—Partial right bundle branch block with small R′. Eight of of the nine patients in this category uniformly followed the above criteria. Because of the low voltage of the RSR′ complex in V_1, the R/S ratios showed a wide variation, being as frequently above unity as below. However, it is of interest that all the R/S ratios in V_{3R} were greater than unity. The preintrinsicoid deflections in V_1 and/or V_{3R} showed about the same range as in Myers and associates'[1] series and were slightly longer than those in "pure" right ventricular hypertrophy.

In these eight patients preintrinsicoid deflections over the left ventricle were shorter than over the right ventricle. Q was not seen in V_{3R}, V_1, or V_2. The value of Lead V_{3R} was well demonstrated, since patterns which were slightly atypical in V_1 showed themselves more fully in Lead V_{3R}. One patient with a

low voltage RSR′ pattern did not conform to the other tracings of this group. Patient W. H. showed a very tall R in V_6, with a preintrinsicoid deflection in V_6 that was similar to that in V_1 and V_{3R}.

Group II B.—Partial right bundle branch block with tall R′. In this group there were eight cases. Six of these had a remarkably uniform pattern, and the two others showed minor differences. In these first six patients the QRS complex varied between .08 and 0.11 second. The RSR′ pattern in V_1 consisted of a small R of 1 to 2 mm., a small S, and an R′ over 7 mm. tall and usually between 10 and 20 mm. The T wave was usually but not invariably inverted in V_1. The preintrinsicoid deflection in V_1 was between 0.50 and 0.69 second in all but one case. The preintrinsicoid deflection in V_6 was between 0.18 and 0.33 second. One patient with a rather short preintrinsicoid deflection in V_1 (0.43 second) was included in this group since all other electrocardiographic characteristics were typical.

Two patients did not fall into the above pattern. In one (E.K.) V_1 showed no typical RSR′ pattern, but due to counterclockwise rotation the RSR′ pattern appeared in V_{3R} and V_{4R}. Also, because of counterclockwise rotation, Q appeared first in V_4 instead of the usual V_6, V_7, or V_8. Hence, because of rotation and displacement of the transitional zone to the right, the preintrinsicoid deflection of V_6 was greater than normal, but not greater than that in V_{3R}.

The second patient (R. S.) showed a borderline widening of QRS in V_1, and probably represented a transitional tracing between partial and complete right bundle branch block. There was no true RSR′ pattern, but a small Q in V_1 and rather prominent slurring of the upward limb of R. This patient represented the closest approximation in the entire series to the classic pattern of right bundle branch block. Tachycardia during this tracing probably influenced the width of the QRS interval.

Group III.—This group consisted of nine cases. Etiologically they represented varieties of congenital heart disease in which both the right and left sides of the heart may be involved equally, giving rise to the so-called "balanced" electrocardiogram. For example, three patients had a patent ductus arteriosus, and three, an interventricular septal defect. Of the nine tracings two were normal, using the standards of Sokolow and associates[10] for adults and Switzer and Besoain[11] for children. The electrocardiograms of five were interpreted as showing bilateral ventricular hypertrophy in varying degree. In each of these tracings the R wave of V_1 and/or the R of V_6 exceeded the normal limit. There was no reversal of the R/S ratio in V_1. Since left ventricular hypertrophy may in itself increase the depth of S in V_1, it is evident that the V_1 R/S ratio will be masked by coexistent hypertrophy of the left ventricle. It is of interest that two patients with patent ductus arteriosus showed this pattern of bilateral ventricular hypertrophy, an unusual electrocardiographic finding in this disease. Of the two remaining tracings, Patient C. S. showed the RSR′ pattern of partial right bundle branch block in V_1 and an abnormally tall R in V_6. M. G., a patient with coarctation of the aorta, showed evidence of pure left ventricular hypertrophy.

SUMMARY

Our purpose in this communication has been to describe the electrocardiogram in the presence of known right ventricular hypertrophy. Calculation of the total work of the right ventricle showed that in all patients work was elevated above the normal. Thus the presumption was made that a degree of right ventricular hypertrophy was present. All patients in this series showed elevation of right ventricular systolic pressure, some with increased flows, and an occasional normal to reduced flow. In two patients not included in this series the electrocardiogram showed right ventricular hypertrophy in the presence of increased cardiac output but with normal right ventricular and pulmonary artery pressures.

Correlation coefficients were calculated relating mean right ventricular pressure and right ventricular work with the R/S ratio in V_1 and the preintrinsicoid deflection time in V_1. None of these factors appear to be mathematically related since the highest correlation coefficient between the right ventricular mean systolic ejection pressure and the height of R in V_1 was plus 0.334, a barely significant figure. Even this degree of correlation is open to question because of the markedly skewed distribution of RV_1. These low correlations in no way negate the clinical significance of the patterns themselves.

The electrocardiogram in congenital heart disease, as recently noted by Uhley[12] and previously by Schnitker,[13] shows few etiologically specific patterns. Predominant involvement of the right side of the heart is a classic characteristic of most types of congenital heart disease. Therefore, in this series, it is not surprising that thirty-five patients have shown electrocardiographic evidence of predominantly right ventricular involvement. Etiologically, the catheterization findings in these thirty-five patients have confirmed the diagnoses of tetralogy of Fallot, tetralogy of Eisenmenger, atrial septal defect, pure pulmonary stenosis, transposed pulmonary veins, atrial or ventricular septal defects with pulmonary stenosis, and the high ventricular septal defect.

All of these thirty-five patients, it should be emphasized, belong in our electrocardiographic Groups I and II. Thus, the electrocardiographic pattern of predominantly right ventricular hypertrophy may show one of two general forms: the classic pattern, with tall RV_1 and marked reversal of the R/S ratio of V_1, may be present; or alternately, a pattern of partial right bundle branch block may appear. If left ventricular enlargement is subordinate, the electrocardiogram of right ventricular hypertrophy should be present in one of these two forms. These two electrocardiographic patterns are not specific for a particular structural diagnosis, and do not appear to be related to the height of the ventricular pressure or work.

It should be emphasized that in this series when right ventricular work is increased in "right-sided" congenital heart disease the electrocardiogram has always been abnormal. Conversely, when the pattern of right ventricular hypertrophy appears in congenital heart disease we may assume an elevated right ventricular pressure or flow. This series, thus, is not comparable with Johnson and associates'[2] group of patients with chronic pulmonary disease, where normal

electrocardiograms were present in some patients having a moderate elevation of mean pulmonary artery pressure. It is to be expected that patients with congenital heart disease would demonstrate more abnormal electrocardiographic findings. For example, the upper limits of our R/S ratios in V_1 are higher than those of either Johnson's or Myers'.

The electrocardiographic pattern of partial right bundle branch block is a relatively new concept and introduces a real problem. We are only prepared to say that it appears with great frequency in the presence of elevated right ventricular work. Whether it represents a mild conduction defect in the right bundle branch, or whether it is a secondary result of the hypertrophy, cannot be decided on the evidence at hand. We do have a larger percentage of tracings in this category than has been reported by Johnson or Myers and their associates. We doubt whether the presence of septal defects is a significant contributory factor in these tracings.

The anatomic diagnoses in Group III differ from those in Groups I and II. Of these nine patients, two tracings were normal, and the one patient with coarctation of the aorta showed left ventricular hypertrophy. Electrocardiograms in the remaining six patients showed findings suggestive of both right and left ventricular enlargement. Because of this bilateral involvement, the typical right ventricular hypertrophy pattern did not appear, being modified significantly by the presence of electromotive forces simultaneously arising from the enlarged left ventricle. Thus, a so-called "balanced" electrocardiogram was inscribed.

CONCLUSIONS

1. The electrocardiographic tracings of forty-four patients with elevated right ventricular pressure due to congenital heart disease have been analyzed.

2. In the thirty-five patients with structurally predominant right ventricular hypertrophy, two electrocardiographic patterns invariably appeared: (1) the "classical" pattern with marked reversal of the R/S ratio in V_1, and (2) varying forms of partial right bundle branch block. In this series, these two patterns have occurred with about equal frequency.

3. There was no specific electrocardiographic pattern associated with any structural abnormality.

4. In our patients with congenital heart disease, patterns of right ventricular hypertrophy and partial right bundle branch block were invariably associated with increased right ventricular work. No relationship could be established between these patterns and the degree of elevation of right ventricular pressure or work.

5. In the nine patients with structural involvement of both right and left ventricles, six electrocardiograms reflected this bilateral hypertrophy.

6. The study emphasizes the diagnostic value of the electrocardiogram in congenital heart disease with right ventricular hypertrophy. Unequivocal hypertrophy patterns (including partial right bundle branch block) are almost invariably associated with increased right ventricular work. The role of the

electrocardiogram in reflecting right ventricular hypertrophy and work is far greater in congenital heart disease than in acquired heart disease such as chronic cor pulmonale.

We are indebted to Miss Mary Mayo for her technical assistance.

REFERENCES

1. Myers, Gordon B., Kline, Howard A., and Stoffer, Burt E.: The Electrocardiographic Diagnosis of Right Ventricular Hypertrophy, AM. HEART J. **35**:1, 1948.
2. Johnson, John B., Ferrer, N. Irene, West, John, and Cournand, Andre: The Relation Between Electrocardiographic Evidence of Right Ventricular Hypertrophy and Pulmonary Artery Pressure in Patients With Chronic Pulmonary Disease, Circulation **1**:536, 1950.
3. Cournand, A., Baldwin, J. S., and Himmelstein, A.: Cardiac Catheterization in Congenital Heart Disease, New York, 1949, The Commonwealth Fund.
4. Griffith, George C., Cosby, R. S., and Levinson, D. C.: Cardiac Catheterization, Univ. So. Calif. Med. Bull. **1**:9, 1949.
5. Griffith, George C., Cosby, R. S., and Levinson, D. C.: Cardiac Catheterization, California Med. **72**:1, 1950.
6. Cournand, A.: Recent Observations on the Dynamics of the Pulmonary Circulation, Bull. New York Acad. Med., second series, **23**:27, 1947.
7. Gorlin, R., and Gorlin, S. G.: Hydraulic Formula for Calculation of the Area of the Stenotic Mitral Valve, Other Cardiac Shunts, and Central Circulatory Shunts, I, AM. HEART J. **41**:1, 1951.
8. Gorlin, R., Sawyer, C. G., Haynes, F. W., Goodale, W. T., and Dexter, L.: Effects of Exercise on Circulatory Dynamics in Mitral Stenosis. III, AM. HEART J. **41**:192, 1951.
9. Barker, J. N., and Valencia, F.: The Precordial Electrocardiogram in Incomplete Right Bundle Branch Block, AM. HEART J. **38**:376, 1949.
10. Sokolow, M., and Friedlander, R. D.: The Normal Unipolar Precordial and Limb Lead Electrocardiogram, AM. HEART J. **38**:565, 1949.
11. Switzer, John, and Besoain, M.: Electrocardiogram of Normal Children, Am. J. Dis. Child. **79**:449, 1949.
12. Uhley, Milton H.: The Electrocardiogram in Congenital Heart Disease. (A Postmortem Correlation Study of 53 Cases), Ann. Int. Med. **33**:188, 1950.
13. Schnitker, M. A.: The Electrocardiogram in Congenital Cardiac Disease, Cambridge, Mass., 1940, Harvard University Press.

ASYMPTOMATIC PULMONARY ARTERIOVENOUS FISTULA: REPORT OF TWO CASES SURGICALLY TREATED

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PULMONARY arteriovenous fistula is a comparatively rare entity. Only six cases were reported to have been found at autopsy prior to 1939, when the first clinical diagnosis was reported.[1,2] With increased interest in recent years, the diagnosis has been made more frequently and there are now at least sixty-nine documented cases in the literature.[3] Early recognition of this anomaly has been stimulated in the past decade since newly developed surgical techniques have proved treatment relatively safe and dramatically effective whereas the lesion may produce serious consequences if left untreated. In this paper two asymptomatic cases, diagnosed clinically and treated surgically, are reported with a view to analysis of clinical features.

CASE REPORTS

CASE 1.—A 30-year-old white woman entered the hospital in February, 1952, for investigation of a lesion which had been noted on a roentgenogram of the chest made during a community tuberculosis survey. She was asymptomatic and had always enjoyed excellent health. Family history was noncontributory.

Abnormal findings on physical examination were limited to the chest, except that mild clubbing of the fingers was present. A blowing machinelike murmur was heard in the sixth left intercostal space in the midaxillary line. Its intensity was greatest during inspiration, decreasing markedly on forced expiration. There was faint transmission of the murmur posteriorly; it was separate and distinct from the apical heart sounds. No cyanosis or skin lesions were noted.

Erythrocyte count was 5.03 million per c.mm., with hemoglobin 16.7 Gm. per 100 c.c. Chest roentgenogram showed a small, rounded shadow of increased density measuring approximately 3 cm. in diameter in the posterior basal segment of the left lower lobe. During fluoroscopy this mass was seen to pulsate in rhythm with the heart beat. Laminographic studies revealed large vessels attached to the spherical lesion. An angiocardiogram was not obtained. Average ear oximeter oxygen saturation reading was 94 per cent at rest and 95 per cent when pure oxygen was breathed. Circulation times, arm-to-tongue (Decholin) 17 seconds, arm-to-lung (ether) 10 seconds. Vital capacity was 4.4 liters, 118 per cent of average normal.

It was the decision of the combined Medical-Surgical Staff that surgical resection of the lesion should be performed. At operation a pulsating saccular lesion, measuring approximately 6 cm. in its longest diameter, was found on the lateral aspect of the left lower lobe. Connecting vessels were ligated and severed and a wedge resection was performed.

Gross tissue examination showed a thin-walled subpleural vascular cavity. Roentgenogram of a barium sulfate preparation of the specimen revealed an irregularly spherical density connected to a large tortuous vessel (Fig. 1). When opened, the cavity was found to have a bluish-white

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Received for publication July 7, 1952.

lining through which entered the afferent and efferent vessels (Fig. 2). Microscopically, all elements of the fistula were again noted.

The patient recovered uneventfully. Shortly prior to her discharge, however, she was found to have a persistent murmur inferior to the left scapula. This murmur was very soft and could only be heard when the breath was held in full inspiration. No lesion could be delineated on chest roentgenogram. It was believed that these findings suggested the presence of another small pulmonary arteriovenous fistula which had not been previously noted.

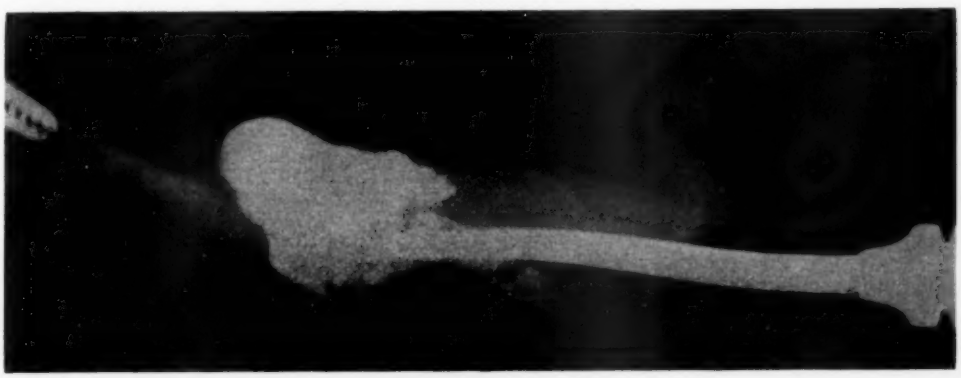

Fig. 1 (Case 1).—Roentgenogram of barium sulfate preparation of fistulous tract. A cannula is inserted through the afferent vessel. (Courtesy of Letterman Army Hospital Photographic Laboratory. Neg. No. L-6742-4.)

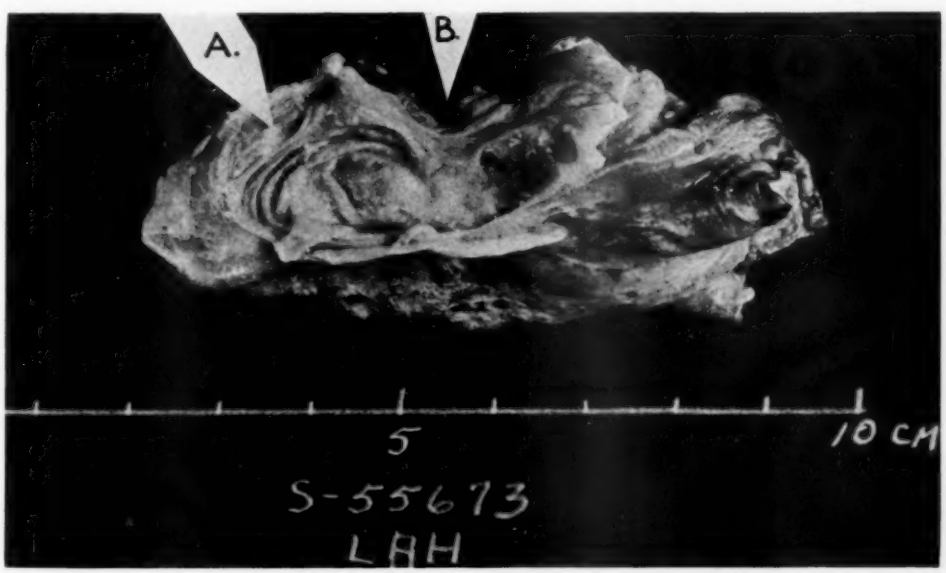

Fig. 2 (Case 1).—Gross surgical specimen of arteriovenous fistula. Arrows indicate (*A*) the afferent and (*B*) the efferent vessels. (Courtesy of Letterman Army Hospital Photographic Laboratory, Neg. No. L-6342-1.)

CASE 2.—A 35-year-old white housewife entered the hospital in March, 1952, because of an abnormality which similarly had been noted on a community tuberculosis survey chest film. She had had an attack of pain in the left side of the chest one month previously, which had been

diagnosed as pleurisy, and had cleared after about six days. Except for feeling that she had always been unusually short of breath on exertion, she had no complaints referable to the cardiorespiratory system. There was no history of cyanosis. Bilateral saphenous vein ligations had been performed in 1950 because of moderately severe varicosities of both lower extremities. A daughter was reported to have skin angiomas; otherwise, the family history was negative for vascular anomalies.

On examination the patient had several tiny hemangiomas over the face and body. A harsh systolic murmur, which was not transmitted, was present in the sixth left intercostal space at the midaxillary line. Deep inspiration increased the intensity of the murmur; on forced expiration it became almost inaudible. No cyanosis or osteoarthropathy was noted. The blood pressure was normal and the heart showed no abnormality to examination.

Chest roentgenogram showed a 2.5 × 3 cm. circumscribed area of increased density in the middle basal segment of the left lower lobe. During fluroscopy this shadow was seen to pulsate regularly. A smaller area of increased density was present medially. It was thought to represent dilatation in the feeder vessel going into the fistulous area. The lesion was again visualized at angiocardiography (Fig. 3), at which time no other fistulas were noted. Hemogram showed 5.02 million erythrocytes per c.mm., and the hemoglobin was 15.9 Gm. per 100 c.c. Circulation time, arm-to-lung (ether) was 9 seconds, and arm-to-tongue (Decholin) was 17 seconds. Arterial oxygen saturation reading, determined with the ear oximeter, was 90 per cent rising to 94 per cent when pure oxygen was inhaled. Vital capacity was 3.4 liters, 106 per cent of average normal.

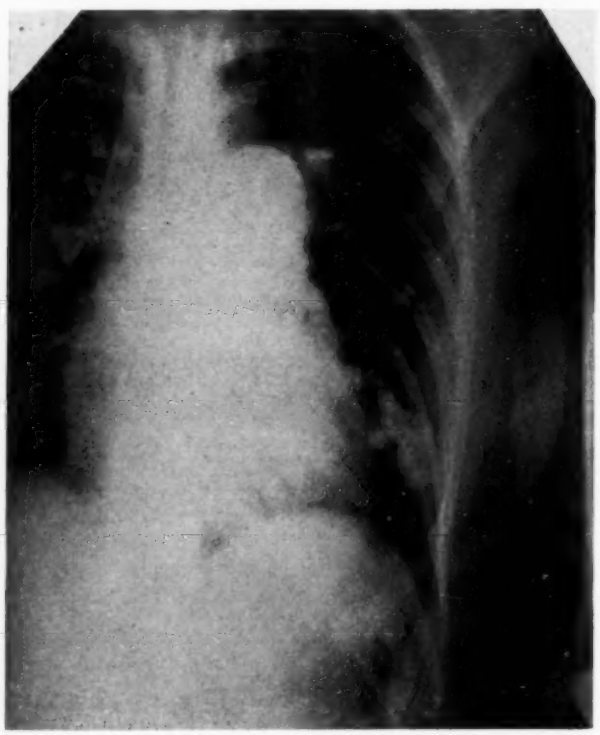

Fig. 3 (Case 2).—Angiocardiogram of arteriovenous fistula in the left lower lobe. There is no evidence of similar anomalies elsewhere.

Surgical removal of the fistula was advised by the combined staff. Thoracotomy revealed a pulsating mass of the size noted on the lateral surface of the left lower lobe. A large vessel entered the fistula on the superior surface. This was dissected free, clamped, cut, and ligated. Wedge

resection of the mass was then accomplished. On gross examination of the excised material a vessel could be traced through an irregular tortuous course into the depths of the specimen, where it opened into a dilated vascular space 1.5 cm. in diameter (Fig. 4). Microscopically all elements of the fistula, with its attached vessels, were clearly seen.

The patient made an uneventful recovery. The chest is now normal to physical examination and roentgenogram.

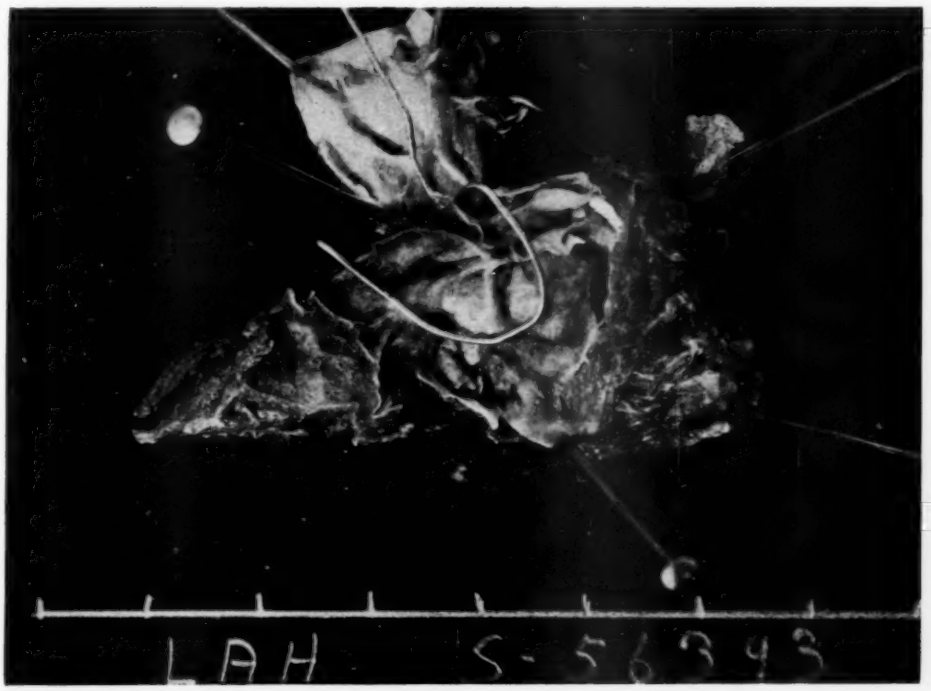

Fig. 4 (Case 2).—Gross surgical specimen. The probe follows the tortuous course of the afferent vessel into the cavity. (Courtesy of Letterman Army Hospital Photographic Laboratory, Neg. No. L-6819-1.)

DISCUSSION

Pulmonary arteriovenous fistula is a congenital anomaly transmitted as a dominant trait with incomplete penetrance.[4] It is probably a variant of multiple hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber's disease) and many of the patients show evidence of hemangiomas or telangiectasia elsewhere on the body. A family history of similar lesions may be obtained in over one-half of the cases.[1,3]

Pathologically, the fistula consists of one or more aneurysmal dilatations in the lung parenchyma, representing an extension of a pulmonary artery which is connected by numerous fistulous vascular channels to a dilated vein. Lesions may occur in any lobe of the lung and are multiple in the majority of cases. No sex predominance has been definitely established. Clinical findings occasionally have been absent,[5-8] but when present are due to a massive shunting of blood from the lesser to the greater circulation. The triad of cyanosis, pulmonary

osteoarthropathy, and polycythemia predominates in the symptomatic case. Exertional dyspnea, precordial pain, weakness, and paresthesia are not uncommon. Epistaxis and hemoptysis may occur.

A bruit usually is heard over the area of the lesion; it may be systolic or extend through all phases of the cardiac cycle as a "machinery" murmur. Typically, the murmur is heard best in full inspiration and may disappear entirely on expiration or on performance of the Valsalva maneuver. Although blood volume is increased in proportion to the degree of polycythemia, a normal plasma volume, heart size, and cardiac output are the usual findings. This is in marked contrast to the physiologic adjustment found in arteriovenous fistulas of the greater circulation, where increase in cardiac output, heart size, and plasma volume are characteristic. It is postulated that this difference is due to the low vascular resistance of the pulmonary bed.[9] In the ordinary case the presence of a shunt would not significantly reduce the over-all pulmonary vascular resistance.

Although many cases of pulmonary arteriovenous fistula may be discovered clinically by the careful observer, the chest roentgenogram is a most valuable diagnostic aid. With the progressive increase in mass population surveys by chest roentgenograms, asymptomatic pulmonary arteriovenous fistulas will be diagnosed with greater frequency in the future. Usually the fistula is represented by a round or lobulated density with sinuous linear shadows representing dilated tortuous afferent and efferent vessels coursing toward the hilum. Pulsation of the lesion and change in its size during the performance of the Valsalva or Mueller maneuvers may be noted on fluoroscopy. Because of the probability of the existence of multiple lesions, angiocardiography is indicated in all cases where surgery is contemplated. A second smaller pulmonary arteriovenous fistula was not diagnosed in Case 1 preoperatively; had angiocardiography been performed, it is conceivable that this lesion might have been discovered. This procedure is also of value in outlining the related vascular elements. Pulmonary arteriovenous fistula may be differentiated from congenital heart disease in that the bruit of the former is extracardiac, it changes in intensity with the respiratory phase, and is usually associated with a heart of normal size. Polycythemia vera may be excluded by the absence of splenomegaly and leukocytosis and the lack of immature cells in the peripheral blood. Tumors, cysts, and inflammatory lesions of the lung may be ruled out by utilization of the radiologic techniques outlined above.

Surgical excision of pulmonary arteriovenous fistulas must be considered in all cases with cyanosis, marked polycythemia, dyspnea, or hemoptysis unless the lesions are so numerous as to make curative surgery impossible. Bloodletting and simple ligation of the feeder vessels are not satisfactory procedures.

In the asymptomatic cases the indications for surgery are not clear cut. The natural course and prognosis of untreated cases have never been clearly delineated. It has been stated that the condition is progressive, as evidenced by increasing cyanosis once it appears and by the fact that the diagnosis is rarely made clinically in childhood.[4] Friedlich and associates[9] showed that in patients with this lesion the vascular resistance of the lung, exclusive of the fistula, is increased. If this is the result of pulmonary arteriolar constriction caused by systemic

hypoxemia, as postulated by Motley and associates,[10] a progressive cycle would result as follows: peripheral arterial oxygen unsaturation would cause increased pulmonary arteriolar constriction, shunting more blood through the fistula, thus producing a further increase in peripheral arterial oxygen unsaturation.

Other possible complications of the untreated case that have been suggested include the ever-present threat of serious hemoptysis and hemothorax,[11] as well as the possibility of peripheral or cerebral thrombosis secondary to the polycythemia, when present.[12] A complicating brain abscess has been reported,[13] as well as a secondary bacterial endarteritis.[14] On the other hand, two cases have been followed twelve and sixteen years, respectively, without demonstrable change in clinical findings or in the size or character of the lesion.[3]

In the cases presented in this paper, decision to remove the lesions was made after careful evaluation of the potentially dangerous consequences of prolonged observation. The facility with which the fistulous areas were resected and the rapid, uneventful recovery of both patients support the validity of the surgical approach.

SUMMARY

Pulmonary arteriovenous fistula, thought to be a rare entity, is being recognized with increasing frequency. The discovery of asymptomatic fistulas will become greater because of the progressive increase in mass population surveys by chest roentgenogram. Two such cases are presented and the problems of diagnosis and treatment are discussed.

REFERENCES

1. Yater, W. M., Finnegan, J., and Giffin, H. M.: Pulmonary Arteriovenous Fistula (Varix), J. A. M. A. **141**:581, 1949.
2. Smith, H. L., and Horton, B. T.: Arteriovenous Fistula of the Lung Associated With Polycythemia Vera: Report of a Case in Which the Diagnosis Was Made Clinically, Am. Heart J. **18**:589, 1939.
3. Seaman, W. B., and Goldman, A.: Roentgen Aspects of Pulmonary Arteriovenous Fistula, Arch. Int. Med. **89**:70, 1952.
4. Goldman, A.: Arteriovenous Fistula of the Lung: Its Hereditary and Clinical Aspects, Am. Rev. Tuberc. **57**:266, 1948.
5. Nightingale, J. A.: A Case of Pulmonary Arteriovenous Fistula, Brit. M. J. **2**:402, 1951.
6. Carswell, J., Jr.: Arteriovenous Fistula of the Lung, J. Thoracic Surg. **19**:789, 1950.
7. Whitaker, W.: Cavernous Hemangioma of the Lung, Thorax **2**:58, 1947.
8. Lindskog, G. E., Liebow, A., Kusel, H., and Janzen, A.: Pulmonary Arteriovenous Aneurysm, Ann. Surg. **132**:591, 1950.
9. Friedlich, A., Bing, R. J., and Blount, S. G., Jr.: Physiologic Studies in Congenital Heart Disease. IX. Circulatory Dynamics in the Anomalies of Venous Return to the Heart Including Pulmonary Arteriovenous Fistula, Bull. Johns Hopkins Hosp. **86**:20, 1950.
10. Motley, H. L., Cournand, A., Werko, L., Himmelstein, A., and Dresdale, D.: The Influence of Short Periods of Induced Acute Anoxia Upon Pulmonary Artery Pressures in Man, Am. J. Physiol. **150**:315, 1947.
11. Bowers, W. F.: Rupture of Visceral Hemangioma as Cause of Death, With Report of a Case of Pulmonary Hemangioma, Nebraska M. J. **21**:55, 1936.
12. Rodes, C. B.: Cavernous Hemangiomas of the Lung With Secondary Polycythemia, J. A. M. A. **110**:1914, 1938.
13. Wodehouse, G. E.: Hemangioma of the Lung: A Review of Four Cases, Including Two Not Previously Reported, One of Which Was Complicated by Brain Abscess due to H. Influenzae, J. Thoracic Surg. **17**:408, 1948.
14. Maier, H. C., Himmelstein, A., Riley, R. L., and Bunin, J. J.: Arteriovenous Fistula of the Lung, J. Thoracic Surg. **17**:13, 1948.

STUDIES IN MITRAL STENOSIS. III. OBSERVATIONS ON THE INCIDENCE AND DISTRIBUTION OF CEREBRAL EMBOLI WITH REGARD TO THE POSSIBILITIES OF THEIR PREVENTION DURING OPERATIVE PROCEDURES

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ONE OF the major dangers in the surgical treatment for mitral stenosis is cerebral embolism. Hemiparesis is obviously a great menace to patients with difficulties of respiration, causing further atelectasis and hypoxia in the postoperative state. Prevention of cerebral embolization by compression of the right carotid artery has been advised by Baker and associates[1] or of both carotid arteries by Harken and associates.[2] We have considered to be of interest the testing of the rationality of such procedures, partly by studying 10 years' material of autopsies from the Department of Pathology, University Hospital, Lund, and partly by experimental studies on the rabbit. So far, we have investigated the relative distribution of emboli in the right and the left hemisphere in mitral stenosis and in experiments; however, studies on the effect of procedures aiming at partial occlusions of one or both carotid arteries for short periods are in progress. This article deals with the first part only. The examination of the autopsy material was performed by P.H. and the experimental studies by S.J.D.*

CEREBRAL EMBOLISM IN MITRAL STENOSIS

(An analysis of 240 autopsies on subjects with valvular heart disease)

A perusal of the literature shows that, although there are several works dealing with the incidence of cerebral embolism in mitral stenosis, very little attention has been paid to the relative distribution of emboli in the right and left hemispheres. This is easily understood, as the problem has had no practical significance until the last few years. Previous studies[3,4,5] indicated that cerebral embolism predominantly affected the left cerebral arteries, a statement which is corroborated by Boyd.[6]

We have examined the autopsy reports for the period 1940 to 1949 from the Department of Pathology of the University Hospital, Lund. The total number of autopsies was 5,300. Of these, 240, or 4.5 per cent, had valvular heart disease.

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Received for publication July 17, 1952.

*We wish to acknowledge the support of Professor C. G. Ahlström, Department of Pathology, University Hospital, Lund, and Dr. O. Axén, Department of Radiology, Allmänna Sjukhuset, Malmö.

No patients with clinical or patho-anatomic evidence of syphilis were included in this figure. These 240 cases were equally distributed between both sexes (120/120).

The incidence of rheumatic valvular disease varies considerably in different parts of the world. The figure, 4.5 per cent, in our material may seem somewhat low in comparison with some statistics from the New England section of the United States,[7,8] but it is in good agreement with the figures from the 1950 material of valvular heart disease at the Malmö General Hospital, recently published by us.[9]

The distribution of the various types of valvular lesions is seen in Table I. The valvular lesions are divided into four groups, the first (I) including all "pure" affections of the mitral valve, the second (II) combined mitral and aortic valvular defects, and the third (III) all "pure" aortic defects. The fourth (IV) is a mixed group with all kinds of combinations of mitral, aortic, and tricuspid valvular diseases. The second and largest group is divided into four subgroups: (A) predominant mitral lesions, (B) minor defects of the same degree in both orifices, (C) major lesions of the same degree in both orifices, and (D) predominant aortic lesions.

TABLE I. ANATOMIC DISTRIBUTION OF VALVULAR DEFECTS IN AUTOPSY MATERIAL

I		II								III		IV	
		MITRAL AND AORTIC											
MITRAL		A. PREDOMINANT MITRAL		B. BOTH EQUALLY SLIGHTLY AFFECTED		C. BOTH EQUALLY SEVERELY AFFECTED		D. PREDOMINANT AORTIC		AORTIC		THE REST	
♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
19	59	15	20	14	11	13	12	16	2	33	10	9	7
32.5%		14.5%		10.4%		10.4%		7.5%		18.0%		6.7%	
47.0%				43.0%									

Clinical statistics from the literature generally show a marked predominance of pure mitral lesions (DeGraf and Lingg[10] 62.5 per cent, Cabot[11] 51.5 per cent, Willius[12] 77 per cent, and Grant[13] 44 per cent). In our previous report,[9] the corresponding figure was 54 per cent. Clinical statistics, however, are apt to overestimate pure mitral lesions and to underestimate minor aortic involvement, which is often discovered only at autopsy. In our present investigation, the figure for pure mitral lesions is 32.5 per cent, which is very close to the figure,

34 per cent, given by Clawson and associates.[14] However, if Group II A (predominant mitral lesions) many of which may clinically appear as pure mitral lesions, is added, the figure is raised to 47 per cent.

Of these 240 patients, twenty-six were shown at autopsy to have cerebral embolism (10.8 per cent). In three cases this was bilateral. According to DeGraf and Lingg,[10] embolism, infarction, and thrombosis are the cause of death in 9.2 per cent of valvular heart disease. Another 10 per cent had arterial embolism with other localization chiefly in kidneys, spleen, the superior mesenteric artery, and the brachial artery. These figures are probably minimum figures, as some of the autopsies were incomplete.

Table II shows the distribution of cerebral emboli in relation to the different valvular defects. Eighty per cent of the emboli were found in cases with a mitral valvular lesion, while emboli in pure aortic lesions were rare. Of these 80 per cent one-half (40 per cent) occurred in the cases of pure mitral stenosis and there was no obvious difference in the distribution on the two hemispheres. Table III clearly demonstrates that the main source of cerebral embolism was found in patients with severe mitral valvular lesions. Embolism was not infrequent below the age of 50 years. There was no difference in the occurrence of cerebral embolism between the sexes.

TABLE II. CEREBRAL EMBOLI IN DIFFERENT VALVULAR LESIONS

LESIONS	♂		♀		TOTAL	
	RIGHT	LEFT	RIGHT	LEFT	RIGHT	LEFT
Mitral	1	2	5	2	6	4
Mitral + aortic						
A. Predominant mitral	3	2	3	4	6	6
B. Both equally slightly affected			1	2	1	2
C. Both equally severely affected	1	1			1	1
D. Predominant aortic						
Aortic		1				1
The rest			1		1	
Totals	5	6	10	8	15	14

The other one-half (40 per cent) was found in the group of combined lesions with predominant mitral valvular lesions (Group II A). Also, this group showed an even distribution of emboli between the right and left sides. As shown in Table IV, this group included some cases of emboli in rather young people.

The remaining 20 per cent also had lesions of the mitral valve, but in combination with lesions in the aorta or in the tricuspid valve (Groups II B, C and Group IV). Only in one case of cerebral embolism was there a pure aortic lesion (Group III).

Most workers agree that surgical treatment is most likely to be of value in patients who are less than 50 years old and where the mitral orifice admits one finger at the most. In our material, five men and eight women (13 patients altogether) belonged to this group. This corresponds to 5 per cent of the total

material of valvular defects or approximately 10 per cent of the patients with clinical mitral stenosis, which very closely conforms with our previous calculations.[9] Of these thirteen patients, not less than five died from cerebral embolism, approximately 40 per cent, a figure which may be relevant to the discussion of the indications and contraindications for the operation of mitral stenosis.

It appears clearly from the tables that cerebral embolism is common in mitral valvular lesions and more frequent the more severe the lesion. No significant differences between right and left cerebral embolism were found in our material.

TABLE III. AGE DISTRIBUTION AND INCIDENCE OF EMBOLI RELATIVE TO SEVERITY OF LESION IN PURE MITRAL VALVULAR DISEASE

AGE (YEARS)	DILATED ORIFICE		NORMAL-SIZED ORIFICE WITH SCLEROSIS		APPROXIMATELY ONE FINGER		LESS THAN ONE FINGER		TOTAL	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
70 and over				5		7(1)	1	2(1)	1	14(2)
60 to 69		1(1)		5		2	3(1)	9(2)	3(1)	17(3)
50 to 59		1	1	1	2	4	1	8(1)	4	14(1)
40 to 49		1				3	2(1)	2(2)	2(1)	6(8)
30 to 39	1		1	1				3	2	4
20 to 29	1				1				2	
10 to 19				2						2
9 and under			5	2					5	2
Totals	2	3(1)	7	16	3	16(1)	7(2)	24(6)	19(2)	59(8)

Figures within parentheses indicate number of emboli.

TABLE IV. AGE DISTRIBUTION AND INCIDENCE OF EMBOLI RELATIVE TO SEVERITY OF LESION IN COMBINED MITRAL-AORTIC LESIONS (PREDOMINANTLY MITRAL)

AGE (YEARS)	DILATED ORIFICE		NORMAL-SIZED ORIFICE		APPROXIMATELY ONE FINGER		LESS THAN ONE FINGER		TOTAL	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
70 and over	1					2			1	2
60 to 69		1				2(3)	1(1)		1(1)	3(3)
50 to 59					1	5(1)	1	2(1)	2	7(2)
40 to 49					3	2(3)	1(1)	2(1)	4(1)	4(4)
30 to 39					2(1)		1	1	3(1)	1
20 to 29		2			2(2)		1		3(2)	2
10 to 19	1								1	
9 and under						1				1
Totals	2	3			8(3)	12(7)	5(2)	5(2)	15(5)	20(9)

Figures within parentheses indicate number of emboli.

PERIPHERAL DISTRIBUTION OF EMBOLI, AFTER INJECTION OF EMBOLIC MATERIAL INTO LEFT HEART OF RABBITS

The vascular characteristics of the aortic arch in man are rare in animals. As far as we know similar conditions exist only in cloacal animals, certain kinds of bats, sirenians, sea cows, and half-apes. The difficulty in procuring such animals necessitated the use of some other experimental animals, for instance, rabbits, in which both the right and the left carotid arteries originate in the innominate artery. The experimental conditions thus are not quite satisfactory; however, this is probably of little consequence. The results obtained in the experiments are in conformity to those of the autopsy findings.

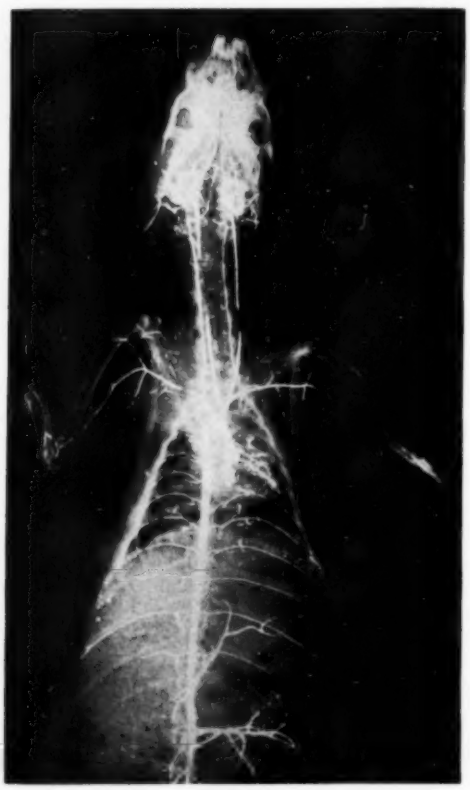

Fig. 1.

The rabbits were about 3 months old and at that age the diameter of the carotid vessels is 1.5 to 2 mm. A rabbit board was utilized throughout and the head of the animal was on the same level as the trunk. Ether anesthesia was used and in a few instances also barbiturates. Heparin was administered prior to the injection of emboli in order to prevent clotting. All injections were made percutaneously into the left ventricle. Identification of the emboli was carried out by means of roentgenograms in several projections. In our first experiments mercury was injected (Fig. 1). In spite of the high specific gravity of this

substance a beautiful contrast picture of the cerebral and other vessels was obtained. However, the mercury did not enter the carotid vessels if the head was raised approximately 60 degrees. Later on, pieces of aluminum (specific gravity 2.7) were injected, of which 30 per cent were traced in the cerebral vessels.

The main part of our experiments was carried out by means of specially constructed "emboli" which were added to a saline solution. The emboli were made from a cellulose sponge with fine pores impregnated with a mixture of lead acetate and glue. The size of the emboli was 0.8 × 0.6 × 0.3 mm. and the specific gravity about 1.5. The number of emboli injected varied from 8 to 65. The percentile recovery varied somewhat in spite of their roentgen opacity. Those which were re-found would be clearly seen and there was usually no difficulty in their identification. There is no reason to believe that the missing emboli were distributed in a manner other than that of those recorded.

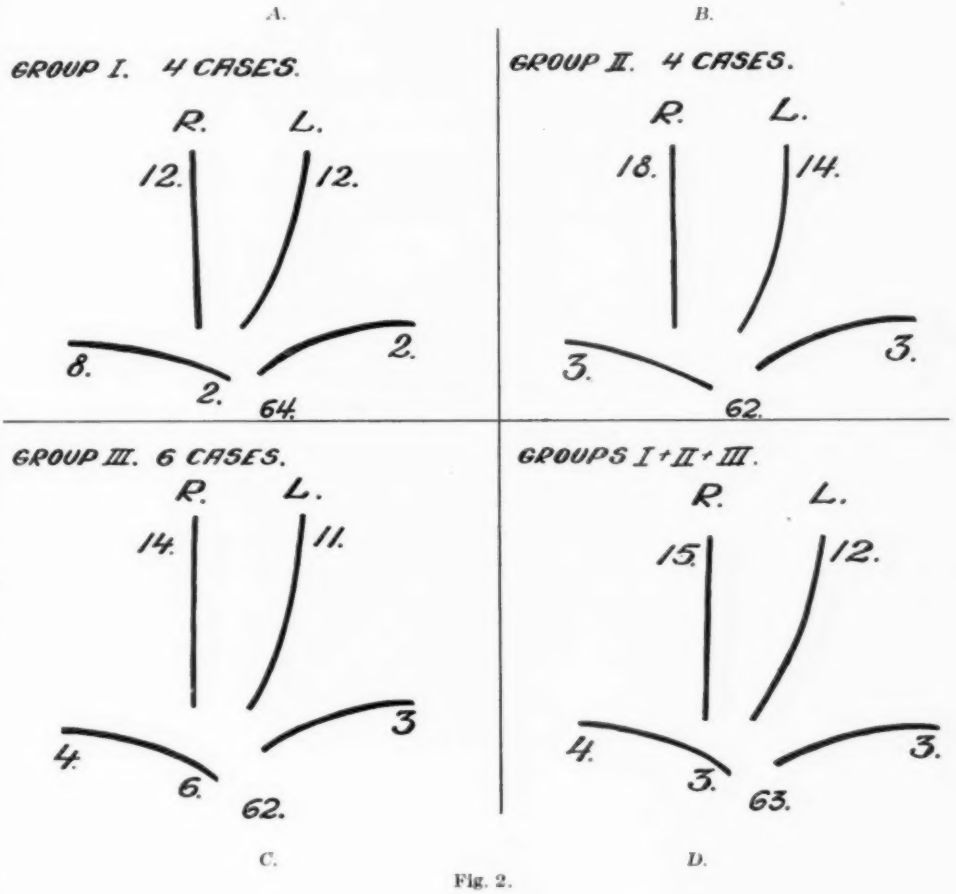

Fig. 2.

Our material is comprised of fourteen successful animal experiments. They were divided into three groups according to the number of emboli found. Group I consisted of four animals. In two of these all emboli were found and in the other two all but one. Groups II and III were comprised of four and six animals;

the number of emboli not traced varied in the second group between 11 and 20 per cent, and in the third between 22 and 53 per cent. The results appear from the sketches (Fig. 2, *A* to *D*), where the figures denote the percentage of emboli in whole numbers. Group I (*A*) showed an even distribution on the two hemispheres, 12 per cent; 8 per cent were found in the right subclavian artery, 2 per cent in the innominate artery, and 2 per cent in the left subclavian artery. In 64 per cent the emboli were spread within the arterial system below the heart. Groups II and III (*B* and *C*) showed a slight predominance of the right hemisphere with 4 and 3 per cent, respectively. In the second group no emboli were observed in the innominate artery but in the third group there were 3 per cent. The fourth sketch (*D*) is a summation of the fourteen experiments. The difference per cent between the right and the left hemisphere was shown to be 3. There appeared furthermore to be a slight predominance of the right subclavian artery as compared to the left. The 3 per cent localized to the innominate artery must be regarded as potential right-carotid emboli since most emboli were situated above the origin of the left carotid artery. However, the difference between the right and left hemispheres was so small that it lends support to the clinical observation of an equal distribution on the two sides.

The total number of cerebral emboli in the three groups was 24, 32, and 25 per cent, the mean being 27 per cent. These figures were somewhat too small in view of the emboli which were located in the innominate artery. The percentage of emboli found in the caudal parts of the vascular system agreed remarkably well in the three groups, thus corroborating the assumption that the emboli not traced were distributed in the same way as the ones traced.

These results are presented as a complement to the autopsy investigation. They will, furthermore, be used as a normal material, forming a starting point for experiments intended to show how the occlusion of one carotid artery affects the distribution of the emboli. Such studies are in progress and the results will be published later. At present, it may be assumed that successful temporary occlusion of one of the carotid arteries will probably reduce the number of cerebral emboli to one-half. Occlusion of one vessel may, however, force the emboli to choose a neighbor vessel, and it may be that occlusion of the right carotid artery will give a somewhat increased embolization through the left carotid artery or through the vertebral arteries.

SUMMARY

Investigations have been carried out on autopsy material, and experimentally on rabbits, in order to ascertain whether cerebral emboli are equally distributed in the right and left hemispheres. Both the autopsy material and the experiments showed that the distribution is even and that no significant predominance of one vessel to the other exists.

REFERENCES

1. Baker, C., Brock, R. C., and Campbell, M.: Valvulotomy for Mitral Stenosis, Brit. M. J. **1**:1283, 1950.
2. Harken, D. E., Ellis, L. B., Dexter, L., Farmand, R. E., and Dickson, J. F.: The Responsibility of the Physician in the Selection of Patients With Mitral Stenosis for Surgical Treatment, Circulation **3**:349-362, 1952.

3. Wegelin, C.: Ueber Aneurysmata dissecanta bei puerperaler Eklampsie, Berl. klin. Wchnschr. pp. 2094-2096, 1909.
4. Savaliew, N.: Gehirnembolie, Archiv für Pathologische Anatomie und Physiologie **135:**112-135, 1894.
5. Hultquist, G. T.: Ueber Thrombose und Embolie der Arteria carotis und hierbei vorkommende Gehirnveränderungen. Papers from St. Erik's Hospital, Stockholm, 1942.
6. Boyd, W.: Textbook of Pathology, ed. 5, Philadelphia, 1948, Lea & Febiger.
7. Davis, D., and Weiss, S.: Rheumatic Heart Disease. I. Incidence and Role in the Causation of Death, AM. HEART J. **7:**146-156, 1931.
8. Harrison, T. R., and Levine, S. A.: Notes on the Regional Distribution of Rheumatic Heart Disease in the United States of America, South. M. J. **17:**914, 1924.
9. Biörck, G., Hall, P., och Jansson, I.: Synpunkter på 1950-års vitiematerial vid Malmö Allmänna sjukhus, Svensk Läkartidning **48:**2214-2225, 1951.
10. DeGraf, A. C., and Lingg, C.: The Course of Rheumatic Heart Disease in Adults, AM. HEART J. **10:**459-486, 1935.
11. Cabot, R. C.: Facts on the Heart, Philadelphia, 1926, W. B. Saunders Company.
12. Willius, F. A.: A Study of the Course of Rheumatic Heart Disease, AM. HEART J. **3:**139-145, 1927.
13. Grant, R. T.: After-histories for Ten Years of a Thousand Men Suffering From Heart Disease. A Study in Prognosis, Heart **16:**275-483, 1933.
14. Clawson, B. J., Bell, E. T., and Hartzell, T. B.: Valvular Diseases of the Heart With Special Reference to the Pathogenesis of Old Valvular Defects, Am. J. Path. **2:**193-232, 1926.

RESULTS OVER A TWO-YEAR PERIOD ON THREE EXPERIMENTAL DIURETICS ADMINISTERED ORALLY TO PATIENTS WITH CARDIAC FAILURE

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LABORATORY[1] and clinical evaluation[2] has indicated that three mercurial compounds, 3-chloromercuri-2-methoxypropylurea (1347Ex)*, 3-carboxymethylmercaptomercuri-2-methoxypropylurea (1353Ex), and 3-(α-carboxyethylmercaptomercuri)-2-methoxypropylurea (1431 Ex), possess diuretic potency greater than Mercuhydrin when compared on the basis of mercury contents. For this reason, further clinical investigation of these compounds was undertaken. During the former studies the drugs were administered parenterally, whereas in the present study they were given orally to patients presenting heart failure in the hope that these drugs would be more effective than oral mercurial diuretics in current use, and could replace parenteral therapy entirely.

METHODS AND PROCEDURE

Initially, eighty-five patients who were being treated for heart failure were selected from the cardiac clinic. At a later date the number of patients studied was increased to 117. The etiology of their heart failure was varied (Table I) and consisted of arteriosclerotic heart disease, rheumatic heart disease, syphilitic heart disease, and hypertensive cardiovascular disease. The functional capacity of each patient was graded from I to IV according to the classification of the American Heart Association. All were on a low-salt diet in so far as this can be regulated on patients in a medical outclinic. They had been followed in the general medical and cardiac clinics for six months to two years prior to the present study, at which time weight charts were maintained. During this control period all of the patients were considered to be as well compensated as possible on an outclinic basis. None of the patients in this study were treated initially with the oral diuretics. They all had required digitalis and from one to two intramuscular injections of Mercuhydrin each week for the past six months in order to maintain cardiac compensation. Immediately before the experimental diuretics were started, a complete blood count, blood urea nitrogen determination, urinalysis, chest roentgenogram, and electrocardiogram were obtained on each

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Received for publication June 10, 1952.

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patient. These were repeated at bimonthly intervals during the study unless otherwise indicated.

The original eighty-five patients were divided into three equivalent groups. The only change in the therapeutic regimen was to replace the parenteral mercurial diuretic which they previously were receiving with one of the three experimental oral preparations. Thirty-five patients (Group I) were placed on 1353Ex; twenty-seven (Group II) were placed on 1431Ex, and twenty-three patients (Group III) were placed on 1347Ex. All of these patients were given one tablet (equivalent to 10 mg. mercury) three times a week regardless of which experimental diuretic they received. The patients returned to the clinic every week, at which time their weight and a brief interval history was obtained. If an increase in weight of more than 3 pounds occurred, or if symptoms of toxicity or progressive failure appeared, the patients were examined thoroughly. Otherwise, a complete examination was made only every one to two months. The electrocardiogram, blood urea nitrogen, urinalysis, and blood counts were repeated at the same time.

Since the smaller doses of all of the diuretics proved to be inadequate, the dose was subsequently increased until the majority of the patients who continued to take the drug orally were receiving eight tablets (equivalent to 80 mg. mercury) per day (two tablets with each meal and two at bedtime). During the initial three months when the low dosage schedule was followed, many of the patients developed failure. Consequently, some of them were lost from the study through hospitalization, the necessity of parenteral drugs, etc. Therefore, when the dosage schedules were increased, additional patients, who had not previously received the drugs, were added to the study. Thus, of the twenty-seven patients receiving 1353Ex and twenty receiving 1431Ex in amounts equivalent to 80 mg. of mercury per day, eight and six, respectively, were new patients. The number of patients who developed failure on 10 mg. of the diuretics three times per week but were subsequently placed on the larger doses are presented in the footnotes to Table I. Because of evidence[2] that 1347Ex is somewhat more active than the other two experimental diuretics, it was studied in more detail. Therefore, the results on intermediate doses with 1347Ex are also presented in Table I. Of the twenty-three patients receiving the small dose of 1347Ex, only ten received the large 80 mg. dose (20 mg. four times a day). However, in addition, ten patients were started on 80 mg. (20 mg. four times a day) as an initial dose and an additional eight patients were started out on a 30 mg. dose (10 mg. three times a day), which was subsequently increased to 60 mg. (20 mg. three times a day). Upon completion of the studies on the three diuretics, placebos were substituted for the experimental diuretics on all patients who appeared to be controlled. Other therapeutic measures, such as digitalis, diet, etc., were not altered. The fact that some patients did not require diuretics in addition to other cardiac therapy at the termination of the study does not indicate that the patients originally were not in heart failure nor that they had not required diuretics for maintaining compensation during the control period. Rather, it indicates that over a period of time a certain number of patients improved their cardiac reserve and had developed a state of semiremission so that

TABLE I. CLINICAL RESPONSE TO THREE EXPERIMENTAL MERCURIAL DIURETICS

PATIENTS (NO.)	DRUG SCHEDULE [a]	DURATION TREATMENT (MOS.)	CONTROLLED		CONTROLLED [b] ON PLACEBOS		FUNCTIONAL CAPACITY [c]				DIAGNOSIS			
			NO.	PER CENT	NO.	PER CENT	+	++	+++	++++	RHD	ASHD	SYP.	HCVD
35 [d]	1353Ex 10 mg.t.i.w.	3 [e]	11	31	6	17	6	14	14	1	3	13	6	13
27 [f]	1353 Ex 80 mg.q.d.	9	26	96	—	—	—	11	15	1	2	10	3	12
27	1431Ex 10 mg.t.i.w.	3 [g]	9	33	6	22	9	8	9	1	3	10	4	10
20 [h]	1431Ex 80 mg.q.d.	6	16	80	2	10	3	9	7	1	3	9	2	6
23	1347Ex 10 mg.t.i.w.	3 [g]	7	30	4	17	4	6	10	3	3	12	3	5
8	1347Ex 30 mg.q.d.	3	3	37	—	—	2	1	3	2	1	2	2	3
8 [i]	1347Ex 60 mg.q.d.	9 [j]	7	88	—	—	2	1	3	2	1	2	2	3
10	1347Ex 80 mg.q.d.	9	9	90	2	20	3	2	4	1	1	6	1	2
10 [k]	1347Ex 80 mg.q.d.	9	9	90	—	—	—	4	5	1	—	6	1	3

Key:
Controlled. Indicates control of manifestations of heart failure equivalent to the control obtained with intramuscular (Mercuhydrin) diuretic administered twice a week.
RHD Rheumatic heart disease.
ASHD Arteriosclerotic heart disease.
SYP. Syphilitic heart disease.
HCVD Hypertensive cardiovascular disease.
t.i.w. Three times per week.
q.d. Every day.

[a] Dose expressed in the amount of mercury contained in each dose.
[b] Refers only to diuretic, not to concurrent therapy for heart failure.
[c] Criteria of American Heart Association.
[d] Two patients died during the study, one with a coronary occlusion and the second with progressive failure which did not respond to either oral or parenteral diuretics.
[e] This regimen discontinued after one month in twelve patients because of progressive failure.
[f] Nineteen of these twenty-seven patients previously had developed progressive failure on 10 mg. three times a week.
[g] This drug schedule discontinued in six patients after one month or less because of progressive failure.
[h] Fourteen of these patients previously developed failure on 10 mg. three times a week.
[i] Same patients who previously received 30 mg.
[j] This schedule discontinued within two months in one patient because of progressive failure.
[k] These are ten patients who previously developed progressive failure on 10 mg. three times a week.

diuretics were no longer necessary. This will occur in a certain number of patients in any group who are adequately treated for heart failure. The only way that the number of patients who had improved to this extent could be determined was to substitute placebos for the experimental diuretic at the completion of the study. The results of this aspect of the evaluation are also presented in Table I. Patients who received the small (10 mg. three times a week) dose of the oral diuretics and were subsequently controlled on placebos were immediately dropped from the study. Conversely, the patients continued in the study and receiving the larger doses of the drugs represented a more severely ill group of cardiac patients.

RESULTS

Results With the Three Oral Diuretics Given Three Times per Week in Amounts Equivalent to 10 mg. Hg per Dose.—Unless otherwise stated, the dose of the diuretic referred to indicates the amount of mercury in milligrams which represents about one-half the weight of the compound. The results are presented in Table I. Thirty-five patients were started on 1353Ex and twenty-seven on 1431Ex in amounts of each diuretic equivalent to 10 mg. mercury. Within one month, twelve of the thirty-five patients receiving 1353Ex and six of the twenty-seven patients receiving 1431Ex had developed progressive failure. By the end of three months, about two-thirds of the patients on each drug had relapsed into failure. Twenty-three patients were started on 10 mg. of 1347Ex three times a week. Within one month, six of the twenty-three patients developed failure and were taken off this regimen. After three months, all but seven were in failure. Of the seven patients who did not develop failure, four were controlled on low-sodium diet, digitalis, and placebos which were substituted for the diuretic. This indicated that diuretics were probably not necessary in at least one-half of the patients who were controlled. The results with the patients controlled on the other two experimental diuretics were similar when placebos were substituted for the diuretic. It thus became evident that this diuretic dosage schedule was inadequate for the treatment of cardiac failure, and after three months this low-dose regimen was discontinued entirely. Throughout the study, it was necessary to evaluate the entire clinical status of the patient, rather than weight gain alone, when attempting to determine increasing heart failure. Progressive weight gain as an indication of increasing failure was valid in only 65 per cent of the patients. The other 35 per cent showed clinical evidence of progressive failure (edema, pulmonary râles, dyspnea, hepatomegaly) without weight gain in excess of 3 pounds. This was probably due to the chronicity of the study and to the fact that food and water intake was decreased when the patient felt ill, so that despite extracellular fluid retention and increased blood volume the net result reflected very little change in weight in some patients.

Results on Larger Doses of 1353Ex (80 mg. Hg/day).—Despite this relatively large dose of diuretic (equivalent to 80 mg. Hg), serious toxic reactions were infrequent and the patients appeared better stabilized. This is best seen by referring to Tables I and II. Of twenty-four patients developing cardiac failure on the small dose of 1353Ex administered three times per week, nineteen were

‡This schedule discontinued within two months in one patient because of progressive failure.
•These are ten patients who previously developed progressive failure on 10 mg. three times a week.

subsequently placed on a dosage schedule of 80 mg. per day (20 mg. four times a day). All but one of these were then controlled. In addition, eight other patients who were started out on this larger dose were well controlled over a period of nine months. The only serious toxic manifestations were abdominal cramps and diarrhea (Table II) seen in four patients. The diarrhea was explosive in nature and was usually more severe in the patients who were given an initial large dose of diuretic. It was less pronounced if the dose of the drug was small at first and was then gradually increased over a period of several weeks. The abdominal cramps were usually completely but temporarily relieved with each bowel movement. One patient experienced nausea and vomiting, and one exhibited rather marked anorexia. However, it was necessary to discontinue the drug in only two patients. Therefore, 1353Ex appeared to be quite effective as an oral diuretic. There were no changes in the electrocardiograms or in blood examinations. The urine showed albumin from time to time, but this was seen just as frequently during the control periods on these same patients.

TABLE II. TOXIC MANIFESTATIONS DUE TO EXPERIMENTAL DIURETICS*

PATIENTS (NO.)	DRUG[a] SCHEDULE	NO. PATIENTS SHOWING DRUG TOXICITY				DRUG DISCONTINUED DUE TO TOXICITY
		NAUSEA AND VOMITING	DIARRHEA	SORE MOUTH	ANOREXIA	
35[e]	1353Ex 10 mg.t.i.w.	1	3†	—	1	1
27[e]	1353Ex 80 mg.q.d.	1	4‡	3	1	2
27	1431Ex 10 mg.t.i.w.	1	—	2	—	—
20[g]	1431Ex 80 mg.q.d.	1	1	5‡	—	2
23	1347Ex 10 mg.t.i.w.	1	2	—	—	—
8	1347Ex 30 mg.q.d.	1	1†	—	—	1
8[h]	1347Ex 60 mg.q.d.	—	2†	—	—	1
10	1347Ex 80 mg.q.d.	—	4†	—	1	1
10	1347Ex 80 mg.q.d.	1	2†	—	—	1

*See Table I for key to abbreviations.
†Oral diuretic discontinued in one patient because of this toxic manifestation.
‡Oral diuretic discontinued in two patients because of this toxic manifestation.

Results on Larger Doses of 1431Ex (80 mg. Hg/day).—The results with the larger doses of this diuretic were quite similar to 1353Ex, except that it appeared to be less effective since only 80 per cent of the patients were controlled. Mouth lesions appeared more frequently, but this may well have been due to a higher incidence of poor oral hygiene in this group. Diarrhea was seen infrequently.

There was no evidence of cardiac or nephrotoxicity. It became necessary to discontinue the drug in two patients because of ulceration of the mandibular mucosa (Table II).

Results on Larger Doses of 1347Ex (30 to 80 mg. Hg/day).—Of the twenty-three patients initially receiving 10 mg. 1347Ex three times a week, sixteen developed failure. Ten of these were then placed on 80 mg. per day (20 mg. four times a day) and all but one (90 per cent) were controlled. Of eight patients receiving 30 mg. mercury in 1347Ex (10 mg. three times a day) over a period of three months, only 37 per cent were controlled, thus indicating that this dose was also inadequate. No change percentagewise was noted when the dose was increased to 40 mg. mercury per day. When the dose in these same patients was increased to 60 mg. mercury (20 mg. three times a day), 88 per cent were controlled. In addition, nine of ten patients who were started on large doses (80 mg. per day—20 mg. four times a day) initially were well controlled. These results indicate that 1347 Ex is a satisfactory oral diuretic if given in adequate amounts. The effective and dependable dose appears to be about 60 to 80 mg. Hg per day. At this dosage level, serious toxic manifestations (Table II), such as cardiac and nephrotoxicity, did not appear, as far as could be determined by urinalysis and electrocardiography. There was no evidence of blood dyscrasia. However, gastrointestinal manifestations occurred in about one-fourth of the patients. In three out of twenty-eight patients, diarrhea was serious enough to require discontinuation of the diuretic. Five additional patients experienced intermittent diarrhea which was tolerable and the diuretics were continued. It was a definite clinical opinion among the authors that the diarrhea was more severe when the patients were started out on a large initial dose than when the initial dose was small and subsequently increased over a period of four to eight weeks. Although gastrointestinal disturbances had a high nuisance value and limited the usefulness of these diuretics somewhat, there were no permanent untoward effects. As soon as the diuretics were discontinued in those patients showing disturbances in gastrointestinal function, this abnormality returned to the control state.

CONCLUSIONS

1. A clinical study has been carried out on one chloromercurial (1347Ex) and two mercaptomercurial (1353Ex and 1431Ex) diuretics administered by the oral route since previous studies have shown them to be decidedly more potent mole for mole than Mercuhydrin.

2. The amount of diuretic required for maintenance was equivalent to 60 to 80 mg. Hg per day when used to replace parenteral diuretics in cases of severe cardiac failure.

3. There was very little difference in diuretic potency or toxicity noted between 1353Ex (3-carboxymethylmercaptomercuri-2-methoxypropylurea) and 1347Ex (3-chloromercuri-2-methoxypropylurea). Diuretic number 1431Ex [3-(α-carboxyethylmercaptomercuri)-2-methoxypropylurea] was less toxic but was also inferior as an oral diuretic.

4. Diuretic number 1347Ex (Neohydrin) if given daily in amounts which contain 60* to 80 mg. Hg can be expected to control approximately 90 per cent of patients with cardiac failure about as well as 1 to 2 c.c. of Mercuhydrin[3] twice a week. If given in this higher dosage schedule, about one-fourth of the patients may develop gastrointestinal symptoms. The drug was discontinued in about 10 per cent of the patients because of this manifestation. However, there are no residual untoward reactions and as soon as the diuretic is discontinued gastrointestinal function returns to normal. Therefore, because of the ease of oral administration as compared to parenteral administration, and because this compound is much more potent than oral mercurials in current use,[3] a more extensive trial of 1347Ex (Neohydrin) administered by the oral route is indicated.

REFERENCES

1. Handley, C. A., Chapman, D. W., and Moyer, J. H.: Some Pharmacological Properties of Three New Mercurial Diuretics, Proc. Soc. Exper. Biol. & Med. **78**:433-437, 1951.
2. Moyer, J. H., Handley, C. A., and Seibert, R. A.: Clinical Diuretic Studies on Three New Mercurial Compounds, AM. HEART J. **44**:281, 1952.
3. Greiner, T., Gold, H., Warshaw, L., Polumbo, F., Weaver, J., Mathes, S., and Marsh, R.: Bioassay of Mercurial Diuretics by Oral Administration in Cardiac Patients With Congestive Failure, Federation Proc. **2**:352, 1952.

*This amount of mercury is contained in 110 mg. (six tablets) of the diuretic.

THERAPEUTIC AND TOXIC EFFECTS OF A NEW ORAL DIURETIC (1-PROPYL-3-ETHYL-6-AMINOURACIL)*

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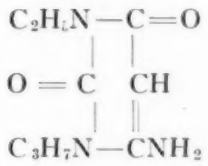
THE OBJECT of this study was to determine the effects of a new oral diuretic in patients with heart failure. The drug is a uracil derivative which contains no mercury:



METHOD

The drug was administered in tablet form to twenty-six ambulatory patients with heart failure who visited the Cardiac Clinic once or twice weekly. In all cases it was given with meals in an effort to reduce gastric irritation. All but two of these patients had been on maintenance digitalis with injections of Thiomerin once or twice weekly for three to twelve months prior to the beginning of this study, and it was determined that their weights were stabilized. In these cases the digitalis was continued and placebo injections were substituted for the Thiomerin. This treatment was maintained until a substantial gain in weight occurred, and the new drug was then added to the regime. The remaining two patients were first seen in marked decompensation, and in these administration of the drug was begun immediately.

The daily dose varied from 0.5 Gm. to 1.5 Gm. divided into three equal doses. In most cases the drug was continued until maximum weight loss occurred. It was then stopped and the patient allowed to regain most of the lost weight. At this point the drug was readministered. In this manner most of the cases received two to three trials.

Response to the drug was judged mainly by weight loss, although diminution of edema and decrease in dyspnea were also evaluated. Thus, results were classified as "good," where there was a loss of 5 to 10 pounds with striking improvement of edema and dyspnea; "fair," where there was a loss of 5 to 8 pounds with only moderate clinical improvement; and "poor," where neither weight loss nor improvement in symptoms occurred.

From the Cardiac Clinic, Gouverneur Hospital, New York, N. Y.
Received for publication June 25, 1952.
*Supplied by Dr. Irwin C. Winter, Division of Clinical Research, G. D. Searle & Co., Chicago, Ill.

TABLE I

CASE NO.	AGE (YRS.)	ETIOLOGIC TYPE HEART DISEASE*	DAILY DOSAGE		RESULTING WEIGHT LOSS (LB.)	TOXIC SYMPTOMS	RESULTS
			AMOUNT (Gm.)	DURATION (DAYS)			
1	32	R.H.D.	(a) 1.5	7	15	Hourly vomiting first day only	Complete relief of dyspnea and 3 plus edema
			(b) 1.5	7	13	Clogging of ears	2nd trial 3 mos. later. Patient had regained 10 lb.
2	70	A.S.H.D.	(a) 1.125	2	4	None	Marked improvement in dyspnea. Complete relief of 2 plus edema
			(b) 1.125	2	3	None	Excellent clinical improvement
3	36	R.H.D.	1.125	5	10	Dizziness	Complete relief of dyspnea and 3 plus edema
4	70	A.S.H.D.	(a) 1.5	7	12	None	Complete relief of 3 plus edema
			(b) 1.5	12	12	None	Complete relief of 2 plus edema
			(c) 1.5	12	12.5	None	Complete relief of 2 plus edema
5	62	A.S.H.D.	(a) 1.5	1	None	Anorexia. Severe nausea and vomiting. Patient stopped drug after 1 day	
			(b) 1.5	6	12	Anorexia. No nausea or vomiting	4 plus edema reduced to 2 plus
6	48	S.H.D.	(a) 1.0	6	11	None	Complete relief of 2 plus edema
			(b) 1.125	7	5	None	Complete relief of 1 plus edema
26	42	R.H.D.	0.75	7	10	Severe epigastric distress, nausea, and vomiting	3 plus dyspnea reduced to 1 plus. Complete relief of 2 plus edema
8	57	Cor pulmonale	(a) 0.75	5	9	None	Complete relief of dyspnea and 2 plus edema
			(b) 1.5	6	7	None	
			(c) 1.5	14	15	Epigastric distress	3 plus edema reduced to 1 plus
			(d) 1.0	10	12	None	2 plus edema reduced to 1 plus
			(e) 1.5	9	None	None	No improvement with drug; 2 c.c. Thiomerin resulted 4 lb. loss. Developed rapid progressive decompensation. Death 2 weeks later
9	58	H.H.D.	1.125	14	5	None	Complete relief of dyspnea and 3 plus edema

9	58	H.H.D.	1.125	14	5	None	Complete relief of dyspnea and 3 plus edema
7	65	H.H.D.	(a) 1.0	10	1	Epigastric distress	After 1st trial, 2 c.c. Thiomerin 2 times weekly for 1 month resulted in loss of 10 lb.
			(b) 1.5	3	3	Severe epigastric distress, headache, dizziness	Thiomerin stopped and patient allowed to gain 8 lb.
			(c) 1.5	20	8	None	Marked diuresis with relief of dyspnea
			(d) 1.5	7	6	None	Marked diuresis with relief of dyspnea
15	62	A.S.H.D.	(a) 1.5	8	8	Severe nausea and vomiting	Complete relief of 2 plus edema
			(b) 1.5	7	3	None	Marked diuresis
12	62	A.S.H.D.	1.5	19	8	None	Slight clinical improvement
10	68	A.S.H.D.	(a) 1.5	24	5	None	2 plus edema unchanged
			(b) 1.5	22	6	None	2 plus edema reduced to 1 plus
			(c) 1.5	27	8	None	2 plus edema reduced to 1 plus; 2 c.c. Thiomerin 2 times weekly for 2 weeks gave no further weight loss
11	68	A.S.H.D.	(a) 1.5	16	5	Nausea, vomiting, dizziness	
			(b) 1.5	9	12	None	Weight found to vary 10 lb. without medication. Patient reported marked diuresis
			(c) 1.125	7	4	Epigastric distress	
13	36	R.H.D.	1.125	7	6	Dizziness	Complete relief of dyspnea. 2 plus edema reduced to 1 plus
14	60	A.S.H.D.	1.5	21	7	None	2 plus dyspnea unrelieved. 3 plus edema reduced to 2 plus
16	57	H.H.D.	1.5	21	None	None	No clinical improvement
17	70	A.S.H.D.	(a) 1.5	17	None	None	2 plus dyspnea unaffected. Previous treatment with Thiomerin resulted in loss of 10 lb. and relief of symptoms
			(b) 1.5	21	None	None	No clinical improvement
18	66	A.S.H.D.	1.0	3	None	Severe epigastric distress, nausea, and vomiting	Patient refused to continue drug
19	65	A.S.H.D.	1.2	7	None	Severe epigastric distress, nausea, and vomiting	Old myocardial infarct

*R.H.D., Rheumatic heart disease. S.H.D., Syphilitic heart disease. A.S.H.D., Arteriosclerotic heart disease. H.H.D., Hypertensive heart disease.

TABLE I (CONTINUED)

CASE NO.	AGE (YRS.)	ETIOLOGIC TYPE HEART DISEASE*	DAILY DOSAGE		RESULTING WEIGHT LOSS (LB.)	TOXIC SYMPTOMS	RESULTS
			AMOUNT (Gm.)	DURATION (DAYS)			
20	60	A.S.H.D.	(a) 1.0	3	None	Headache	1 plus dyspnea unaffected
			(b) 1.5	7	None	Epigastric distress	2 c.c. Thiomerin 2 times weekly for 1 month resulted in 4 lb. loss and relief of dyspnea
			(c) 1.5	14	3	None	2 c.c. Thiomerin 2 times weekly for 3 months resulted in 16 lb. loss with complete relief of dyspnea
21	64	H.H.D.	1.5	21	None	Epigastric distress, nausea, and vomiting	
22	48	H.H.D.	1.5	9	None	None	3 plus dyspnea and 4 plus edema unchanged
23	68	A.S.H.D.	1.125	14	None	Severe epigastric distress, nausea, and vomiting	No clinical improvement
24	70	A.S.H.D.	(a) 1.125	1	2	Patient stopped drug after 2 doses because of severe nausea and vomiting	No clinical improvement
			(b) 0.75	3	None	Patient stopped drug after 3 days because of severe nausea and vomiting	No clinical improvement
25	65	A.S.H.D.	1.125	14	None	Ringing in ears	1 plus edema unchanged. For next 3 weeks 2 c.c. Mercuhydrin once weekly resulted in loss of 7 lb. with relief of edema

*R.H.D., Rheumatic heart disease.
S.H.D., Syphilitic heart disease.
A.S.H.D., Arteriosclerotic heart disease.
H.H.D., Hypertensive heart disease.

RESULTS

In nine of the twenty-six cases (34.6 per cent) response to the drug was considered good. In seven of these, excellent diuresis with loss of 10 pounds or more was obtained. In Cases 2 and 9 a loss of only 6 and 5 pounds, respectively, was noted; but in each instance the clinical improvement was striking (Table I; Fig. 1).

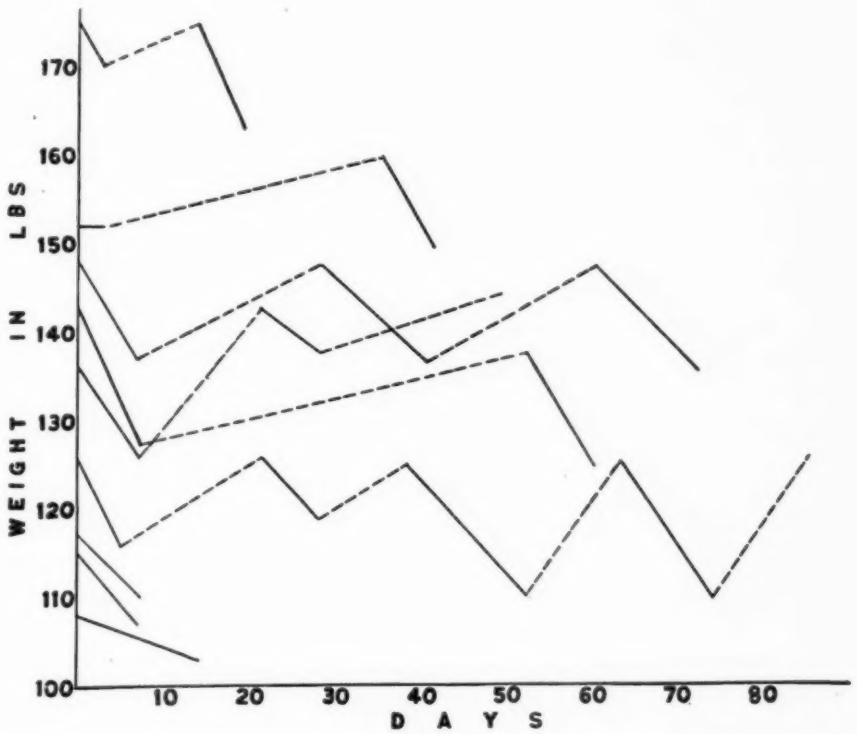


Fig. 1.—Weight curves of patients showing good response to drug. ——, Period during which drug was taken. – – –, Intervals when no drug was taken.

In seven cases (27 per cent) results were classified as fair (Table I; Fig. 2). The remaining ten cases (38 per cent) showed neither weight loss nor clinical improvement (Table I).

TOXIC EFFECTS

Seventeen of the twenty-six cases showed evidence of side effects as follows:

Nausea and vomiting	11
Epigastric distress	10
Anorexia	2
Dizziness	3
Ringing in the ears	2
Headache	1

These symptoms occurred either alone or in combination. In each case they were recorded only if they were of moderate or severe degree. Eight patients refused to continue the drug because of the severity of these symptoms.

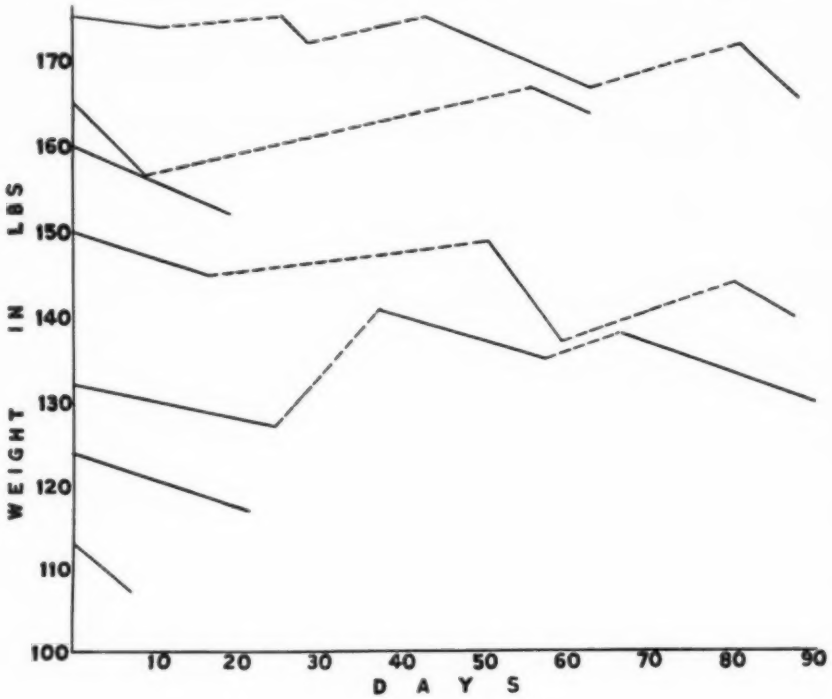


Fig. 2.—Weight curves of patients showing fair response to drug. ——, Period during which drug was taken – – –, Intervals when no drug was taken.

DISCUSSION

For the past few years efforts have been made to find a potent oral diuretic which does not contain mercury. Papesch and Schroeder[2] synthesized forty compounds related to the xanthines. While certain of these exhibited potent diuretic activity, the incidence of toxic side effects was extremely high.

Recent investigation has concentrated upon a group of uracil derivatives in the hope of avoiding these side effects. Van Arman and associates[3] compared the effects of 1-propyl-3-ethyl-6-aminouracil with aminophylline and with Salyrgan in animals. They concluded that there is no great difference in diuretic effect among these compounds of uracil and xanthine structure, and that the maximum effect obtainable is somewhat less than with Salyrgan.

The chief side effect which they noted in dogs was emesis, which occurred six times in twenty-six trials. Therapeutic doses had little or no effect on blood pressure, heart rate, respiration, or intestinal activity. Toxic doses produced evidence of central nervous system stimulation. Lethal doses produced muscular incoordination and convulsions.

Kattus and Newman[1] studied the effect of 1-propyl-3-ethyl-6-aminouracil on sodium excretion in ten subjects with normal cardiac and renal function. They found that the diuretic effect of 1.2 Gm. given in four divided doses during one day was comparable to the effects of an injection of 2 c.c. of Thiomerin. They then administered the drug to fifteen patients with edema due to congestive heart failure and obtained a good diuretic response in eight (50 per cent); a moderate response in three (20 per cent), and no response in four (30 per cent). In only two of these fifteen patients were evidences of toxicity noted, one developing diarrhea and the other vomiting. They also carried out experiments on a dog in order to determine the mechanism of action of the drug and concluded that it acts by inhibiting the renal tubular reabsorption of sodium and chloride.

In a more recent study[4] of thirty-seven cases, excellent diuresis was reported in 54 per cent and moderate response in 19 per cent. The incidence of toxic side effects was low, anorexia occurring in 6 per cent, nausea in 10 per cent, vomiting in 8 per cent, and vomiting and diarrhea in 2 per cent.

In the twenty-six cases reported in this series the results, though somewhat less favorable, are comparable to those reported by Kattus and associates.[4] Evidence of toxicity, however, was noted in the majority of our cases. In some instances these symptoms were so unpleasant that the patients refused to continue the drug. We therefore feel that the clinical usefulness of this preparation is vitiated by the high incidence of toxic side effects.

SUMMARY

1. 1-propyl-3-ethyl-6-aminouracil, a nonmercurial oral diuretic, was given to twenty-six ambulatory cardiac patients in heart failure.

2. A good diuretic response with loss of 10 pounds or more was noted in nine cases.

3. A fair response with loss of 5 to 8 pounds was noted in seven cases.

4. The remaining ten cases showed no response.

5. Seventeen of the twenty-six cases developed toxic side effects. In eight patients these symptoms were severe enough to warrant stopping the drug.

6. It is concluded that this drug is a fairly potent oral diuretic agent, but that the incidence of toxic symptoms is too high to permit its clinical application.

REFERENCES

1. Kattus, A., and Newman, E. V.: Observations on a New Oral Diuretic Compound (1-Ethyl-3-Propyl-6-Aminouracil), J. Clin. Investigation **29**:827, 1950.
2. Papesch, V., and Schroeder, E. F.: Synthesis of Some 1-Mono and 1,3-Diallyl-6-Aminouracils, Presented at the 117th Meeting of the American Chemical Soicety in Philadelphia, April, 1950.
3. Van Arman, C. G., Freese, H. B., Hambourger, H. E., and Green, D. H.: SC-2614 and SC-3088: New Orally Active Diuretic Compounds. In press.
4. Kattus, A., Arrington, T. M., and Newman, E. V.: Clinical Observations on a New Oral Diuretic 1-Propyl-3-Ethyl-6-Aminouracil and Preliminary Studies on 1-Allyl-3-Ethyl-6-Aminouracil, Am. J. Med. **12**:319-330, 1952.

A CLINICAL EVUALATION OF THE TREATMENT OF HYPERTENSION WITH DIHYDROGENATED ERGOTOXINE ALKALOIDS

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THE THERAPY of hypertension by means of dihydrogenated ergot alkaloids was first proposed by Rothlin.[1] Dihydrogenation of one of the five double bonds of the lysergic acid content of the ergotamine and ergotoxine group of ergot alkaloids results in five compounds, three of which possess some qualitatively different actions than the natural alkaloids.[2] Dihydroergotamine and most probably dihydroergosine retain the direct constrictor effect on peripheral vessels, while dihydroergocristine, DCS-90, dihydroergocornine, DHO-180, and dihydroergokryptine, DHK-135, possess predominately sympathicolytic and vasodepressor actions. These hydrogenated compounds are far less toxic than the natural alkaloids, and are markedly hypotensive parenterally, less certainly so when given orally. The fall in blood pressure observed in both experimental animals and man is especially marked in hypertensive individuals. This has been shown to be due to: (1) depression of the central pressoreceptor mechanism and (2) inhibition of peripheral adrenosympathetic action.[1-6] An equal parts mixture of these sympathicolytic derivatives (DCS-90, DHO-180, and DHK-135) termed CCK-179 or Hydergine* is more effective than any of its constituents in lowering blood pressure.[3] CCK-179 given orally, parenterally, and in combination has been favorably reported on in the long-range treatment of hypertension by Kappert,[3] Duret,[7] and others.[8-12]

In view of this reported effectiveness and low toxicity of the drug in the treatment of hypertension, a therapeutic trial of CCK-179 was made on a group of hypertensive patients of Cook County Hospital.

MATERIAL AND METHODS

Thirty-four patients were selected from routine hospital admissions to a general male medical ward on the basis of hypertension in excess of 150 mm. Hg systolic and 100 mm. Hg diastolic, and systemic manifestations of hypertensive disease. Seventeen individuals had frank cardiac decompensation as the pre-

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Supported in part by a research grant from Mrs. Alfred Eustice.

Received for publication July 3, 1952.

*CCK-179 is the laboratory number for Hydergine; it was supplied through the courtesy of Sandoz Pharmaceuticals, Inc., Chicago, Ill.

senting manifestation; eleven, vascular disease of the central nervous system (hemiplegia or diffuse encephalopathy); three, cardiac failure and central nervous disease combined; and three had kidney involvement associated with nitrogen retention.

The general background of most of the patients was one of low income, with poor housing and nutrition. Hospitalization to them was, in general, a definite approximation of a serene and worry-free period of living. All had severe enough symptoms from their hypertension to cause them to seek hospital admission. In twenty-one patients with previous medical attention the average duration of known hypertension was four and one-half years. It varied from no previously known hypertension in four patients to twenty years in one. The average age was 60.7 years and varied from 30 to 78 years.

The patients were questioned and examined carefully; routine electrocardiograms, two meter chest roentgenograms, blood nonprotein nitrogen determinations, complete blood counts, and urinalysis were performed. Further work-up was done as indicated.

All patients were placed at complete bed rest on admission; blood pressure readings (auscultatory) were taken morning and evening. After an initial observation period of ten to fourteen days when an apparent basal blood pressure was reached, oral administration of the drug was begun in increasing doses. This varied from 1 to 16 mg. and averaged 9 mg. The average duration of continuous therapy for hospitalized patients was 24.3 days, while for ambulant patients it was 94.7 days. When the complicating manifestations improved (under appropriate therapy: digitalis, diuretics, low-sodium diet, etc.) sufficiently to permit, the patients were transferred to the ambulatory ward. In this ward, they walked to the toilet and ate in a bedside chair. After a further period of treatment and observation in this ambulant ward, they were discharged home and observed as outpatients. The mean hospital stay was 45.5 days; the mean observation period in the outpatient clinic was 122 days.

In nine hospitalized patients the effect of substituting a placebo for medication was determined. This substitution was unsuspected by the patient, lasted eight days, and all other therapy remained the same. The acute effect of intravenous administration of 0.6 mg. of CCK-179 was studied in thirty individuals.

Thus, the over-all plan of this study was the observation of the blood pressures and clinical status of a group of symptomatic hypertensive patients progressively during (1) admission to a general hospital, (2) hospitalization, (3) hospitalization and CCK-179, (4) placebo medication and hospitalization, (5) CCK-179 and normal living conditions with outpatient visits, and (6) intravenous administration of CCK-179.

RESULTS

1. Changes in Blood Pressure. (Fig. 1).—The arithmetic mean of the blood pressures on admission, thirty-four individuals with forty admissions, was 203/123 mm. Hg. With hospitalization alone the mean of the blood pressures fell 34 mm.

Hg systolic and 18 mm. Hg diastolic to 169/105* in a period of ten to fourteen days. During the period of oral administration of the dihydrogenated ergot alkaloids to the group of thirty patients, the mean pressure continued to fall to 163/102,* 6 mm. Hg systolic, 3 mm. Hg diastolic less than that of the initial observation period. An analysis of the treatment period revealed that this minor fall occurred during the first two weeks of the period. No rise in pressure or change in symptomatology occurred with substitution of a placebo late in the course of treatment; the blood pressures and the end of placebo therapy averaged 161/98 mm. Hg.* Thus, in general, the mean blood pressure level fell rapidly during the beginning of hospitalization, more slowly during the beginning of the course of treatment, then leveled off in about thirty days, and was unaffected by substitution of placebo.

Seventeen of the individuals were followed in the ambulant clinic. Their average pressure after receiving CCK-179 in this status was 185/115 mm. Hg,* an increase of 22 mm. Hg systolic, 13 mm. Hg diastolic, over the hospital treatment period. In every individual case the pressure rose during ambulation, and it was noted that there was a direct relationship between duration of ambulant treatment and the elevation of the blood pressure. While on ambulant therapy four patients were readmitted because of a return of their original symptoms. The initial blood pressure on the second admission was comparable to the initial blood pressure on the first admission. These four patients were placed on bed rest and on the same treatment as on the first admission except that no CCK-179 was given. Under these circumstances the blood pressures fell as rapidly to the same level observed during the prior admission.

2. *Changes in Clinical Manifestations.*—

A. *Cardiac decompensation*: On admission all twenty cardiac patients were classified as Grade III or IV functionally, and Grade E therapeutically (American Heart Association). The usual methods of treatment for congestive failure were employed: digitalis, morphine sulfate, mercurial diuretics, ammonium chloride, and a low-salt diet (less than 1 Gm. Na per 24 hours). There was a rapid improvement in the state of compensation in all individuals and this was maintained during hospitalization. During the outpatient treatment period, symptoms of failure slowly returned and, of the group of twenty, seven have died of cardiac failure.

B. *Central nervous system complications*: The eleven individuals with complicating hemiplegia or encephalopathy were kept at absolute bed rest with no specific therapy until their general clinical condition permitted either ambulation or physiotherapy. Moderate functional improvement resulted from such therapy. Regular clinic follow-up was poorest in this group because of physical handicaps. Of the nine followed, five had recurrence of central nervous system symptoms, and one died.

C. The three patients with *frank uremia* died of this condition. Their hypertension and clinical condition was refractory to all therapy, including CCK-179.

*The pressures used are the mean of the last three days of the respective period being considered, and thus constitute the end result of the particular therapy employed.

D. *Subjective manifestations*: Most individuals claimed improvement within the first week of bed rest alone. In view of the unreliability of such criteria no detailed evaluation of this aspect was made.

3. Acute Hypotensive Effect of Parenteral CCK-179.—Thirty individuals were given 0.6 mg. of the drug intravenously and the blood pressure recorded approximately every ten minutes for two to three hours. All showed a fall in blood pressure during this period and this was accomplished without any signs of mental suppression or drowsiness. The average pressure before injection was 188/110 mm. Hg; the average pressure at its lowest point was 151/90 mm. Hg, a drop of 37 mm. Hg systolic and 20 mm. Hg diastolic. The maximum depression occurred within fifteen to ninety minutes. The pressures returned to original levels within three hours. In seventeen of the group, normal blood pressure levels were reached. Twenty-one individuals reached a blood pressure level distinctly lower than at any other time during the entire course of observation. The only reaction to the parenteral drug consisted of nausea and vomiting in three cases.

4. Toxicity.—Eleven patients of the original group of thirty-four died of hypertensive complications during the period of observation. Careful analysis of these cases revealed no evidence that the drug contributed to death. The sole toxic manifestations from oral administration consisted of nausea and vomiting in three patients, all of whom were receiving 3.0 mg. per day for various periods of time. Much higher dosage for long periods of time failed to produce nausea or vomiting in the remaining patients. Postural hypotension appeared transiently in one patient during oral treatment and in another following parenteral administration.

DISCUSSION

The past few years have seen the introduction of many chemotherapeutic agents in the treatment of hypertension. The value of these drugs has been based upon their hypotensive properties but side effects limit the use of some. The marked increase in heart rate associated with the fall in systemic blood pressure observed with tetraethylammonium salts and Dibenamine limits their value.[5] Penta- and hexamethonium block all the autonomic ganglia with an atropine-like effect when administered parenterally and fail to show constant results when administered orally.[5,13] 1-Hydrazinophthalazine and 4-methyl-1-hydrazinophthalazine are moderately hypotensive but have not been fully evaluated clinically.[14] The value of thiocyanates is probably secondary to its analgesic and sedative action.[15] Among the more promising agents are Veratrum viride derivatives and some of the hydrogenated ergotoxine compounds. Both of these agents are capable of lowering systemic pressure without detrimental circulatory changes. The work of Goetz,[5] Kappert and associates,[3] Gast and Heuber,[8] Duret,[7] and others indicated that dihydroergocornine or, preferably, CCK-179 was highly adaptable to the long-range therapy of hypertension.

The fall in blood pressure following intravenous administration of CCK-179 observed in the present study is in accord with previous reports.[3] CCK-179 produced a definite depression of systolic and diastolic arterial pressure of several

hours' duration in every case, even those with advanced complications. This effect was accompanied by nausea and vomiting in three of the thirty cases. Goetz and Kappert both found this combination of three derivatives more effective in reducing the blood pressure than any of the single ergot alkaloids.

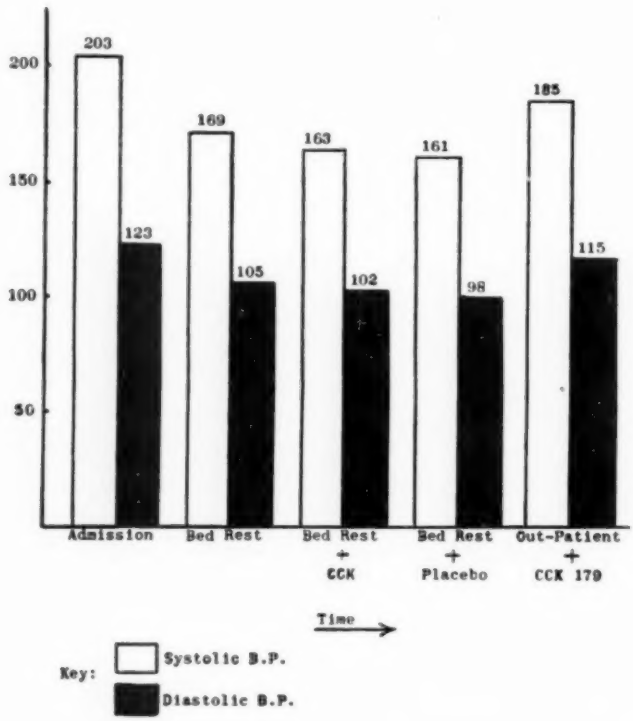

Fig. 1.—Average group systolic and diastolic blood pressures at end of various consecutive periods of observation.

Results of the oral administration of CCK-179, in contrast to its intravenous injection, to our group of thirty-four hypertensive patients were much less striking. During the initial period of hospitalization, the average pressure of the group fell rapidly from 203/123 to 169/105 mm. Hg. It continued to fall more slowly for the first ten to fourteen days of the hospitalization plus CCK-179 therapy, and, after approximately one month of hospitalization, reached a steady level of 40 mm. Hg systolic and 21 mm. Hg diastolic below the admission level. Eight days of placebo substitution during this latter stage after several weeks of CCK-179 therapy produced no rise in pressure. The minor drop in pressure recorded during the therapy period must therefore, be due to continued effects of hospitalization, not CCK-179. This would indicate that in the study of such a group of symptomatic hypertensive patients the basal control period must be at least thirty days, not seven to fourteen days during which the obvious and rapid decrease in pressure due to change to a restful environment occurs.

Discharge to ambulant clinic status and thus return to rather normal home life, while on continuous oral CCK-179 therapy, resulted in a definite and rapid climb in blood pressure. The failure of the drug to reduce blood pressure in ambulant patients differs from the results of Kappert, Duret, and Gast. Reason for this may be found in our selection of patients in the advanced stage of the disease, and the prolonged period (45.5 days average) of hospital bed rest during which we observed these patients. These two factors make the present study a severe test of the value of the oral administration of CCK-179, and are considered essential in the ultimate evaluation of CCK-179 or similar hypotensive drugs. This drug failed to give satisfactory results under these conditions. The authors wish to emphasize the effectiveness of a prolonged period of hospitalization in lowering the blood pressure of hypertensive individuals and the dangers in ascribing this effect to any drug administered during the period.

SUMMARY

1. CCK-179 was administered orally to thirty-four symptomatic hypertensive men.

2. A marked drop of blood pressure occurred during the first thirty days of hospitalization plus therapy. This was shown by placebo substitution to be due to hospitalization, not the drug.

3. Parenteral administration produced a definite but transient drop in blood pressure in all cases to whom it was given.

The authors are indebted to Mr. Ray Rondinelli, Preble Laboratory, for his invaluable contribution to this study, and also to Mr. Harry F. Schnizer of Sandoz Pharmaceuticals, Chicago, Ill., for generous supplies of the drug and constant cooperation.

REFERENCES

1. Rothlin, E.: The Pharmacology of the Natural and Dihydrogenated Alkaloids of Ergot, Bull. Schweitz. Akad. d. med. Wissenschr. **2**:249, 1947.
2. Stoll, A., and Hofman, A.: Die Alkaloide der Ergotoringruppe: Ergocristin, Ergokryptin, und Ergocornin, Helvet. chim. acta. **26**:2070, 1943.
   Stoll, A., Hofman, A., and Petrzilka, T.: Die Dihydroderivative der fechtsdrehenden Mutterkornalkaloide, Helvet. chim. acta. **29**:635, 1946.
3. Kappert, A.: Untersuchungen über die Wirkung neuer dihydrierter Mutterkornalkaloide bei peripheren Durchblutungsstorungen und Hypertonie, Helvet. med. acta., Suppl. XXII, 1949.
4. Wilkins, R. W., Fries, E. D., and Stanton, J. R.: Essential Hypertension, J. A. M. A. **140**:261, 1949.
5. Goetz, R. H.: The Effect of Sympathicolytic Drugs on the Cardiovascular System in Man With Special Reference to Hypertension, Angiology **2**:1, 1951.
6. Blunschli, H. J., and Goetz, R. H.: The Effect of Ergot Derivatives on the Circulation in Man With Special Reference to Two New Hydrogenated Compounds, Am. Heart J. **35**:873, 1948.
7. Duret, R. L.: Action des derives hydrogenes de l'ergot dans l'hypertension arterielle, Acta clin. belg. **6**:85, 1950.
8. Gast, W., and Heuber, E. F.: Ueber die Behandlung der Hypertension mit Hydergin, Wein. klin. Wchnschr. **62**:900, 1950.
9. Josephs, I. L.: Clinical Observations on the Hypotensive Effect of Certain Dihydrogenated Alkaloids of Ergot in Human Beings, Am. Pract. **4**:71, 1949.
10. Gibbs, D. F.: Dihydrogenated Alkaloids of Ergot in the Investigation and Treatment of Diastolic Hypertension, Brit. Heart J. **14**:77, 1952.

11. Sarre, H.: Klinik und Therapie der Hyper- und Hypotonie, Verhandl. d. deutsch. Gesellsch. Kreislauffarsch. forsch. 15. Tagung, 137 (1949).
12. Oderthal, F.: Ueber die Behandlung der Hypertonie mit Hydergin, Deutsche med. Wchnschr. **36**:1907, 1951.
13. Fries, E. D., Finnerty, F. A., Schnaper, H. W., and Johnson, R. L.: The Treatment of Hypertension With Hexamethonium, Circulation **5**:20, 1952.
14. Schroeder, H. A.: The Effect of 1-Hydrazinophthalazine in Hypertension, Circulation **5**:28, 1952.
15. Corcoran, A. C., Page, I. H., Masson, G. M. C., Taylor, R. D., and Dustan, H.: Hypertension and Hypertensive Cardiovascular Disease, Arch. Int. Med. **87**:732, 1951.

Clinical Reports

PULSELESS DISEASE

A Preliminary Case Report

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PULSELESS or Takayasu's disease[1] is considered by Japanese ophthalmologists to be a rare but definite clinical entity. A review of the literature (Tables I and II) revealed fifty-eight reported cases. The syndrome is characterized[2] by loss of pulsations in the radial arteries, absence of detectable blood pressure in the arms, and ocular findings including the progressive formation of peripapillary arteriovenous anastomoses and cataracts. The outstanding presenting symptoms are visual disturbances ranging from photopsia and blurring to blindness, and syncopal attacks which are frequently associated with convulsions. The syncope is attributed to hypersensitivity of the carotid sinus and appears to be induced by turning the head upward or to the side, or by suddenly arising from a supine position. These findings are allegedly the result of thrombosis of the subclavian and carotid arteries secondary to a panarteritis of unknown etiology. It is reported that the microscopic examination of the lesions suggests a tuberculous etiology, but an active etiological agent has not been demonstrated. The retinal arteriovenous anastomoses and cataracts are considered to be the result of chronic circulatory insufficiency.

The following is a preliminary report of a case which is believed to be typical of Takayasu's or pulseless disease. It apparently is the first case to be reported outside of Japan.

CASE REPORT

A 19-year-old married white woman, with the presenting complaint of blindness in both eyes, was examined here on and subsequent to March 18, 1952. She reported that she had been in good health with 20/20 vision in each eye until the summer of 1949 when she began to experience fleeting episodes of syncope and loss of vision. Permanent loss of vision in the right eye developed within a period of 24 hours, and there was progressive loss of vision in the left eye with retention of only light perception by the end of 1949. Concurrently she began to experience syncopal attacks which appeared to be induced by arising rapidly from a supine position, and by suddenly turning the head upward or to either side. In 1949 she underwent a neurosurgical investigation, including

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Received for publication April 29, 1952.
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TABLE I. REPORTED CASES OF PULSELESS DISEASE[3]

REPORTER	YEAR	AGE OF PATIENT (YEARS) AT TIME OF: REPORT	AGE OF PATIENT (YEARS) AT TIME OF: ONSET	SEX	JOURNAL	COMMENTS
M. Takayasu	1908	21	21	F	Acta Soc. Ophth. Jap. **12**:554	Fundus findings, cataract extraction
K. Onishi T. Kagoshima	1908 1908	? ?	? ?	? ?		Absent radial pulse
M. Kondo	1916	18	18	F	J. Army Med. Dept	Absent carotid pulse
M. Nakajima	1921	19	18	F	J. Jap. Ophth. A.	Cerebral symptoms
T. Nakano	1930	15	14	F	J. Jap. Ophth. A.	Slight leukocytosis, positive tuberculin test
T. Furukawa	1935	19	18	F	J. Jap. Ophth. A.	
N. Minekoshi S. Uchiyama	1937	12	11	M	J. Jap. Ophth. A.	Fainting, convulsions, elevated sedimentation rate
S. Tomita I. Azuma	1937	18	18	F	Grenzgebiet	Vagotonia
C. Nagashima O. Kitamoto T. Sato K. Okamura	1937	25	24	F	Klin. Wchnschr. **17**:1154	External carotid and brachial arteries examined histologically; thrombosis found
A. Hayashi S. Nishimaru	1938	27	20	F	J. Psychiat.	Arteriography of carotid and vertebral artery
S. Okamura	1938	15	13	F	J. Jap. Ophth. A.	Diminished aorta pulsation
T. Saito	1939	20	17	F	Exp. Ophth.	
S. Yasuda	1939	34	32	F	Clin. Ophth.	
T. Dodo	1939	22	21	F	J. Jap. Ophth. A.	Lowered pressure in vessels attributed to Buerger's disease
H. Takagi	1940	16	15	F	J. Jap. Ophth. A.	Buerger's disease
T. Tanaka	1940	28	27	F	J. Jap. Ophth. A.	Buerger's disease
S. Uchimura	1940	21 17 18	21 11 17	M F F	J. Tokyo Univ.	Syncope produced by forceful bending of head downward. Presumed to be central type of Buerger's disease
Y. Niimi	1941 1942	17 31	16 27	F F	General Ophth. General Ophth.	Perforated nasal septum
I. Kume	1943	33	27	F	General Ophth.	
K. Ota N. Yui	1943	25	24	F	J. Jap. Path. Soc.	Panarteritis of major arteries of upper half of trunk
K. Shimizu	1948	6 cases			Clin. Surg.	Named this disease "pulseless disease" or thrombo-arteritis obliterans subclavio-carotica, claimed tbc as etiology, established triad-absent pulse, eye changes, carotid sinus sensitivity

TABLE II. REPORTED CASES OF PULSELESS DISEASE[4]

REPORTER	YEAR	AGE OF PATIENT (YEARS)		SEX	JOURNAL	COMMENTS
		AT TIME OF REPORT	AT TIME OF ONSET			
T. Dodo	1949	(12 cases—including case previously reported by Dr. Dodo)				
K. Sudo	1949	30		F	Diag. & Treat.	
M. Yanagida	1950	(11 cases—including 6 cases of Prof. Shimizu's)				
		13		F	Clin. Ophth.	Distinguished three stages:
		20		F		1. Dilating stage of vessels
		37		F		2. Stage of anastomosis
		22		F		3. Stage of eye complication
		10		F		
		23		F		
		20		F		
		17		F		
		24		M		
		45		F		
		19		F		
T. Oba	1950	25	20	F	Medicine	
H. Kato et al.	1951	19	17	F	J. Jap. Med. Soc.	Denied Buerger's disease
		25	13	F		
K. Kinoshita	1951	26	14	M	J. Jap. Med. Soc.	Tuberculosis-like changes in the media of major arteries from aorta
		29	20	F		
K. Yamashita	1951	19	18	F	J. Jap. Med. Soc.	
Y. Yamashita	1951				J. Jap. Med. Soc.	
K. Okuda	1951	24	22	F	Gen. Med.	Pulmonary tuberculosis. Patient was followed from onset of disease
K. Itahara	1952	22	21	F	Jap. Clinic	
		33	22	F		
S. Oishi	1952	39		M	Clin. Ophth.	Aneurysm of radial artery, features of collagen disease

ventriculography, at another institution, and the results were reported to be negative. In September, 1951, following another extensive examination, an intracapsular extraction of the lens of the left eye was performed with only slight improvement in light perception. The ophthalmoscopic examination at that time was reported as showing "sludging of blood in the veins, arteriovenous shunts, and optic atrophy." At the time of her discharge the impression was rendered that she had "an undiagnosed generalized vascular disease." Except for the subsequent development of a cataract in the right eye, and a decrease in the frequency of syncopal attacks, there has apparently been little change in the patient's condition to the present time.

General physical examination in the Department of Medicine revealed a well-developed, well-nourished white woman in no apparent distress except for visual disturbance. Radial, ulnar, temporal, and right carotid artery pulsations could not be felt. Faint pulsation was noted in the region of the left carotid artery, but the vessel could not be palpated. Normal pulsations were present in the femoral, popliteal, dorsalis pedis, and posterior tibial arteries. The blood pressure

could not be measured in either arm, but was measured at 180 mm. Hg over 130 mm. Hg in the leg. The otolaryngologic examination was negative except for the presence of a perforation of the nasal septum. The lungs were clear to auscultation and percussion. The heart was normal in size to percussion, the rhythm was regular, and the rate was 110 per minute. No auscultatory abnormalities were noted in the examination of the heart. The neurological examination was negative except for an equivocal Babinski sign bilaterally, and there was no significant abnormality in the remainder of the physical examination. During the attempt to palpate the left carotid artery, a syncopal attack lasting approximately six seconds was induced; no apparent alteration in the heart rate was observed at this time. Laboratory studies included an erythrocyte count of 4,760,000 per c.mm., a leukocyte count of 9,050 per c.mm.; the hemoglobin measured 11.4 Gm. per 100 ml., and the cell volume 38 c.c. The routine urinalysis was negative as were the Wassermann and Kahn reactions, and the fasting blood sugar measured 94 mg. per 100 ml. By x-ray examination the size and configuration of the heart and aorta appeared to be normal, the barium-filled esophagus was in normal position, and the lung fields were clear. An electrocardiogram demonstrated the presence of sinus tachycardia with an auricular rate of 110, all of the conduction intervals were within normal limits, the T waves were inverted in Leads III and V_1, diphasic in Lead V_2, low and notched in Lead V_4. The electroencephalographic record was of low amplitude without any well-defined alpha pattern. There was little change in the record with hyperventilation and no change suggesting the presence of a focal cortical lesion. It was concluded that the tracing was border line abnormal.

The patient was referred to the Department of Ophthalmology on April 7, 1952, for evaluation of her ocular complaints. The following were the pertinent findings on ophthalmic examination: Right eye: Visual acuity—poor light perception and inaccurate light projection. There was a pearly white mature cortical cataract. On oblique focal illumination no iris shadow was cast. The eye transilluminated well. A spindle-shaped deposit of brown pigment (Krukenberg's spindle) was seen on the posterior surface of the cornea extending from the center to the limbus at 6 o'clock. A fine vessel was visible on the iris at 8 o'clock. A faint orange-red reflex was seen with the ophthalmoscope. Left eye: Visual acuity—hand movements at two feet; light projection, good. A corneal macula was located at the inferior pupillary border. There was a complete surgical iridectomy with surgical aphakia. The remaining iris was thin. Ophthalmoscopic examination revealed a fair orange-red flex. There were fine dustlike vitreous opacities. The fundus proper presented a most unusual sight. The disc was yellowish-white with fairly distinct edges. There was no cupping. The papillary arteries and veins extended out from the disc onto the retina for a distance of 1 to 2 disc diameters. There each artery was seen to form a terminal loop anastomosis with the accompanying vein. This was visible inferiorly, nasally, and superiorly. There was no apparent continuation of the retinal vessels beyond these loops. The choroidal vessels were only faintly visible peripherally through the retina. No hemorrhages or exudates were seen. The macula was clear without a foveolar reflex.

The patient returned to the clinic on May 12, 1952, for a consultation in the Department of Neurosurgery. An additional finding at this time was the presence of an ischemic ulcer on the tip of the nose. The neurosurgical recommendations included the accomplishment of a bilateral carotid sinus denervation and a cervical sympathectomy. These procedures have not yet been carried out.

CONCLUSION

In the case presented there is a distinctive history of visual disturbances and syncopal attacks; objective abnormalities include the absence of arterial pulsations and detectable blood pressure in the arms, and ocular finding of peripapillary arteriovenous anastomoses and cataract. Because of these findings it is considered that the case is representative of Takayasu's or pulseless disease.

REFERENCES

1. Takayasu, M.: Acta. Soc. Ophth. Jap. **12**:554, 1908.
2. Shimizu, K., and Sano, K.: Pulseless Disease, J. Neuropath. and Clin. Neurol. **1**:37, 1951. Abstract, J. A. M. A. **145**:1095, 1951.
3. Shimizu, K.: Pulseless Disease. Rinsho Geka (Clinical Surgery) **3**:377, 1948. (Summary of cases as translated from the Japanese and provided through the courtesy of Kunio Okuda, M.D., Department of Medicine, Yamaguchi Medical College, in a personal communication to W. C. C.)
4. Okuda, K.: Personal communication to W. C. C.

UNILATERAL RENAL ARTERY OBSTRUCTION ASSOCIATED WITH MALIGNANT NEPHROSCLEROSIS CONFINED TO THE OPPOSITE KIDNEY

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FOLLOWING the observations by Goldblatt in the dog concerning the role of renal ischemia in the pathogenesis of hypertension, other workers investigated the effects of unilateral partial renal artery obstruction in rats and rabbits. When sustained hypertension was thus produced, it was found that the opposite, nonischemic kidney revealed the morphologic changes associated with hypertension while the ischemic kidney remained largely free of these alterations. It was noted, however, that unilateral renal ischemia associated with sustained hypertension occurred rarely in man. Few observations, made at autopsy of such patients, are recorded. For this reason, we wish to report the findings in a patient dying with malignant hypertension and renal failure who at autopsy showed partial obstruction of one renal artery. Morphologic changes associated with hypertension were found in the opposite kidney and other organs while the kidney supplied by the partially occluded artery was spared these changes.

CASE REPORT

A 42-year-old white salesman was admitted to the hospital on June 27, 1951, with the complaints of "headache and high blood pressure." In 1943 he had first noted exertional dyspnea and in 1947 he began to experience severe frontal headaches. A physician told him that his blood pressure was "over 220." After six weeks of symptomatic treatment, the patient was free of complaints. The headache and dyspnea returned in January, 1950, but it was not until about two months before admission that the patient sought medical attention. The headaches had become excruciatingly severe, his vision had blurred, and he had fainted on two occasions. A physician noted hypertension and retinal hemorrhages, and he prescribed a low-salt diet and digitalis. This regime was continued until two weeks before admission.

The patient had been previously treated at this hospital for complaints unrelated to his present illness. The blood pressure readings on these occasions were as follows: 1934, 136/84; 1939, 110/70, and 140/100 mm. Hg. The urine on these clinic visits was negative.

Physical examination revealed: Temperature, 99°F.; pulse rate, 100; respiration, 20; blood pressure, 220/140 mm. Hg. The patient showed signs of weight loss and muscular atrophy. The fundi showed hemorrhages, exudates, and moderate papilledema. The heart was enlarged to the left anterior axillary line and a soft systolic murmur was heard at the base. The lungs were clear. The liver edge was felt three fingerbreadths below the costal margin and there was no costovertebral angle tenderness. The neurological examination was negative.

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Received for publication June 20, 1952.

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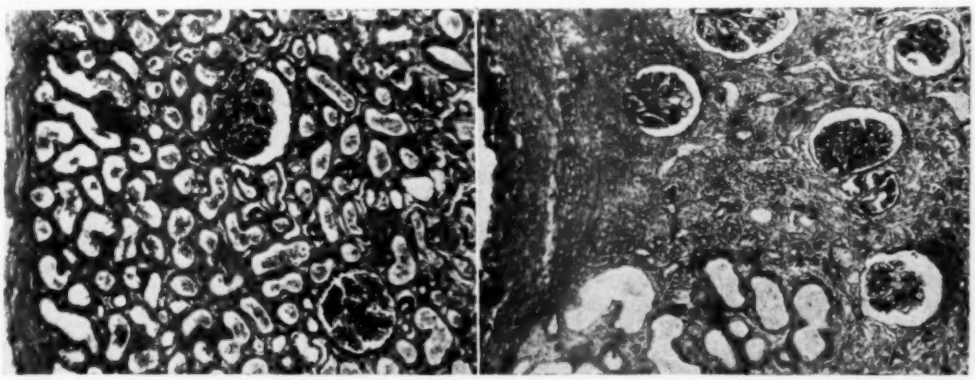
During his hospital course the patient had albuminuria of 1 to 4 plus. The urine specific gravity ranged from 1.018 to 1.020. A few white blood cells were seen in each specimen and there was microscopic and sometimes gross hematuria. The hemoglobin on admission was 18.9 Gm. per cent but fell to levels of 12 to 14 Gm. per cent. The red blood cell count was 5.37 million per $mm.^3$ but fell to levels of 3.0 to 4.0 million. The white blood cell count on admission was 15,950. It soon returned to normal levels and remained there until ten days before death. Thereafter counts of 18,000 to 37,000 were obtained. The blood urea nitrogen on admission was 33 mg. per cent. It fell to 14 mg. per cent on the second day and remained there until ten days before death when it rose rapidly, reaching 191 mg. per cent on the day before death. The serum chlorides ranged from 82 to 86 meq./L.; the serum sodium from 116 to 129 meq./L. and the serum potassium from 4.32 to 6.6 meq./L. On admission the CO_2 combining power was 30 meq./L.



A. *B.*

Fig. 1.—*A*, Left kidney, "protected" by partial occlusion of renal artery. Note the absence of glomerular, tubular, or vascular changes.
***B*, Right kidney, with unimpaired blood supply showing the changes of arteriolonephrosclerosis. (Hematoxylin-phloxin, ×96.)**

The patient received a standard rice diet for thirteen days, followed by a 200 mg. sodium diet which was doubled in ten days and continued until the patient was thought to have a "low salt syndrome." He was then put on a regular diet and for the last six days was given 6 Gm. of sodium chloride daily. Fever therapy was found to be ineffective. Ten days before death the patient became confused and terminally progressed to coma. He died on the fiftieth hospital day.

AUTOPSY

Gross Findings.—The principal autopsy findings involved the aorta and kidneys. The abdominal aorta showed marked atherosclerosis. A few plaques were calcified with an occasional ulceration of the intima. The left renal artery, at its origin, was markedly narrowed by an encircling atheromatous plaque which extended 2.5 cm. distally. The vessel then divided into two branches and the one to the upper pole was occluded by a recent ante-mortem thrombus.

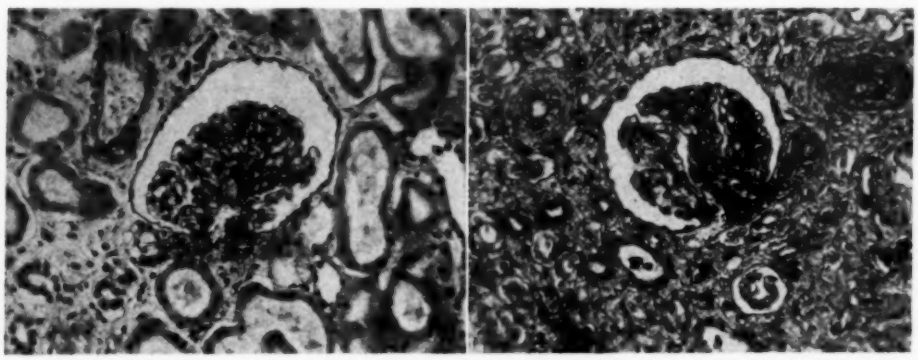
The surface of the left kidney (155 grams) was smooth, showing only rare 2 mm. stellate-depressed areas. A large recent infarct involved the upper pole and a bandlike area of the lateral border. On cut surface the upper two-thirds of the organ was infarcted. The lower pole was normal in appearance with a cortex of 7 to 9 mm. in thickness. The calyces, pelvis, and ureter were normal.

The right renal artery was patent. The surface of the right kidney (135 grams) was pale and coarsely granular. Two small recent hemorrhagic infarcts were seen in the upper pole. The cortex was irregularly narrowed, varying from 3 to 7 mm., and revealed many punctate hemorrhages. The calyces, pelvis, and ureter were normal.

The enlarged heart (665 grams) showed left ventricular hypertrophy and a mural thrombus in the right auricular appendage. The coronary arteries contained atheromatous plaques but were patent throughout. The peripheral branches of the pulmonary arteries showed atheromatous plaques and a few were occluded by recent emboli. A subpleural, hemorrhagic infarct of 2 cm. in diameter was seen in the right lower lobe.

Additional gross findings were: Cystic dilatation of the distal pancreatic duct, cholelithiasis, partial thrombosis of the periprostatic venous plexus, ascites (300 c.c.), and bilateral hydrothorax (300 c.c.).

Histologic Findings.—Sections from the lower pole of the left kidney revealed a normal pattern (Figs. 1,*A* and 2,*A*). The glomeruli presented no changes. The tubules and their epithelium were normal. No arteriolar lesions could be found. The arteries in the medulla showed slight hyaline intimal thickening. The infarcted portion presented recent coagulation necrosis but the ghostlike outlines of the normal landmarks were easily discerned. At the periphery of the infarct, leukocytic infiltration and early fibroblastic response were seen.



A. *B.*

Fig. 2.—*A*, Left kidney. This close-up emphasizes the normal architecture. *B*, Right kidney. Marked changes, involving the glomerulus, arterioles, and tubules are shown. (Hematoxylin-phloxin, ×180.)

In contrast, sections of the right kidney showed widespread arterio- and arteriolosclerosis with extensive necrotizing arteriolitis (Figs. 1,*B* and 2,*B*). The glomeruli were diffusely damaged with lesions ranging from acute fibrinoid degeneration to proliferation of the cells lining the capsule and loops, to complete hyalinization. Many tubules were dilated and their epithelium revealed varying degrees of hyaline and fatty metamorphosis. Hyaline casts were frequent. The interstitial connective tissue was edematous and fibrous. Recent fibrinoid necrosis of the arterioles, particularly at the junction between the afferent vessel and glomerulus was commonly encountered. The larger arteries revealed some hyaline intimal thickening. The areas of infarction also exhibited recent hemorrhagic necrosis as described above.

Necrotizing arteriolitis was found throughout the gastrointestinal tract, in the pancreas, adrenal capsule, and prostate. In addition, the arterioles throughout all organs showed hyaline thickening of their walls. The laminated thrombus found in the left renal artery showed early organization. Histologic examination of the other organs revealed: Infarction and fibrosis of the lungs; chronic passive congestion of the liver, spleen, and other abdominal organs; chronic cholecystitis; acute and chronic pancreatitis, myocardial fibrosis, and atherosclerosis involving the aorta, the coronary, pulmonary, and cerebral arteries.

Anatomic Diagnoses.—Malignant nephrosclerosis of the right kidney; partial infarction of the left kidney due to thrombosis of a main branch of the renal artery; partial occlusion of the left renal artery due to an atheromatous plaque; necrotizing arteriolitis present in the adrenal capsule, pancreas, gastrointestinal tract, and prostate; atherosclerosis of the aorta, pulmonary, coronary,

and cerebral arteries; pulmonary infarction and fibrosis; chronic passive congestion of the liver, spleen, gastrointestinal tract, and lungs; left ventricular hypertrophy; mural thrombus of the right auricular appendage; thrombosis of the periprostatic venous plexus; ascites (300 c.c.); pleural effusion, bilateral (300 c.c.); acute and chronic pancreatitis; chronic cholecystitis, and cholelithiasis.

COMMENT

Wilson and Byrom[2] showed that sustained hypertension could be produced in rats by partial occlusion of one renal artery. They noted that the morphologic changes associated with hypertension were largely confined to the nonischemic kidney. Similar observations were made by Wilson and Pickering[3] in rabbits, and by Byrom and Dobson[4] in rats. Schroeder and Neumann,[5] in a similar experiment, found equal damage in both kidneys. These authors employed ligatures rather than finely adjustable clamps and the difference in technique might account for their results.

Examples of sustained hypertension in man associated with unilateral renal artery obstruction have been extensively reviewed by Yuile.[6] We could, however, find only a few reports in which the vascular changes associated with hypertension occurred only in the nonischemic kidney. In Saphir and Ballinger's[7] patient, an organizing perinephric hematoma compressed the left renal artery which was already partially occluded by a calcified thrombus. The patient described by Schwartz and Gross[8] had Buerger's disease with occlusion of one renal artery without infarction of the kidney it supplied. The patient reported by Aronson and Sampson[9] presented thrombosis of the right renal artery with an essentially normal right kidney, while the left kidney showed necrotizing arteriolitis. Two cases were reported by Yuile.[6] In the first, a kidney removed surgically because of thrombosis of its artery was normal except for small recent infarcts, while the other kidney, examined shortly thereafter at autopsy, was hypertrophied and revealed a necrotizing arteriolitis. Yuile's other patient showed a renal artery occluded by thrombus with a small but histologically normal kidney on this side, while the other kidney was hypertrophied and showed typical arteriolar lesions. Goodman[10] described a case of malignant hypertension with occlusion of the right renal artery and necrotizing arteriolitis in the opposite kidney. Freeman and Hartley[11] reported a patient who was normotensive when he submitted to unilateral nephrectomy following a crushing injury to the kidney. Two years later he developed progressively severe hypertension and died a few months later. At autopsy the artery of the remaining kidney was markedly constricted by an atheromatous plaque. Little vascular damage was seen within the kidney, while the arterioles throughout the other organs bore out the clinical impression of malignant hypertension.

The chief findings in our own case are similar to those in the above-mentioned reports. Long-standing hypertension was associated with partial obstruction of one, the left, renal artery. The left kidney was essentially normal except for a recent large infarct. Necrotizing arteriolitis was present throughout the body, most marked in the right kidney.

As a clinicopathologic correlation, the following course of events could be postulated. In consequence of unilateral renal artery obstruction by an atheromatous plaque, our patient developed sustained hypertension. As this progressed, the vascular and other changes generally associated with severe hypertension involved the entire body, including the right kidney. The left kidney remained "protected" from the systemic disease by its diminished blood supply and thereby escaped damage. The sudden precipitous rise of the patient's blood urea nitrogen ten days prior to death could be attributed to the simultaneous occurrence of renal infarction which no longer permitted the left kidney to maintain adequate function. This loss of excretory capacity in the face of a severely impaired contralateral kidney probably precipitated the rapidly progressing uremia and led to the patient's death.

SUMMARY

A case of unilateral renal artery obstruction, associated with malignant hypertension, is reported. The ischemic kidney showed a massive recent infarct, but was otherwise normal. The striking similarity of this case to results of animal experiments is pointed out.

REFERENCES

1. Goldblatt, H., Lynch, J., Hanzal, R. F., and Summerville, W. W.: Studies on Experimental Hypertension, J. Exper. Med. **59**:347, 1934.
2. Wilson, C., and Byrom, F. B.: The Vicious Circle in Chronic Bright's Disease, Quart. J. Med. **10**:35, 1941.
3. Wilson, C., and Pickering, G. W.: Acute Arterial Lesions in Rabbits With Experimental Renal Hypertension, Clin. Sc. **3**:343, 1938.
4. Byrom, F. B., and Dodson, L. F.: The Mechanism of the Vicious Circle in Chronic Hypertension, Clin. Sc. **8**:1, 1949.
5. Schroeder, H. A., and Neumann, C.: Arterial Hypertension in Rats; Effects on the Kidney, J. Exper. Med. **75**:527, 1942.
6. Yuile, C. L.: Obstructive Lesions of the Main Renal Artery in Relation to Hypertension, Am. J. Med. Sc. **207**:394, 1944.
7. Saphir, O., and Ballinger, J.: Hypertension and Unilateral Malignant Nephrosclerosis, Arch. Int. Med. **66**:541, 1940.
8. Schwartz, N. H., and Gross, S.: Unilateral Malignant Nephrosclerosis, J. Urol. **62**:426, 1949.
9. Aronson, S., and Sampson, M.: Unilateral Benign and Malignant Nephrosclerosis and Cortical Necrosis, Associated With Contralateral Renal Artery Occlusion, Arch. Path. **51**:30, 1951.
10. Goodman, H. L.: Malignant Hypertension With Unilateral Renal Artery Occlusion, New England J. Med. **246**:28, 1952.
11. Freeman, G., and Hartley, G.: Hypertension in a Patient With a Solitary Ischemic Kidney, J. A. M. A. **111**:1159, 1938.

DELAYED CLOSURE OF THE DUCTUS ARTERIOSUS

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AT THE time of birth and in the early neonatal period, there is normally a gradual increase in the amount of blood which passes through the pulmonary vascular tree, and during this period the shunts from the pulmonary circuit to the systemic circuit, which have served their purpose in fetal life, gradually close. The time of complete closure of the ductus arteriosus is variable. Patten[1] has reported that this does not occur before 6 or 8 weeks of age. According to Christie,[2] there is a sharp fall in the incidence of patent ductus arteriosus to 12.0 per cent during the first 8 weeks of life and a more gradual fall to 1.2 per cent during the remainder of the first year, while Gross[3] considers it abnormal for the ductus arteriosus to remain open after the age of 1 year.

If the ductus arteriosus continues to function after the first year of life, circulatory changes develop which create an added burden for both ventricles. When the lesion is uncomplicated, most patients get along quite well, but, if the lesion is large, serious difficulties including congestive heart failure may arise at an early age. Although most patients are asymptomatic and live many years before circulatory difficulties appear, they are always subject to subacute bacterial endarteritis, and surgical treatment with obliteration of the ductus is clearly indicated to eliminate the circulatory defect and the hazard of infection.

Occasional instances of delayed spontaneous closure of the patent ductus arteriosus have been reported, and, although the exact incidence of this phenomenon cannot be determined, judging from the small number of such reports it must be rare. Gross[3] speculated that late closure of the patent ductus may be one of the reasons for the low incidence of patent ductus arteriosus in adults as compared with the incidence in children. Reid,[4] in his discussion of the paper by Gross, suggested that perhaps some children who have been considered to "outgrow" a cardiovascular lesion had a patent ductus arteriosus which closed spontaneously.

Williams[5] probably reported the first case of delayed closure of a patent ductus arteriosus. The age of this patient was not given, but the patient had exertional dyspnea and a typical continuous murmur. Thus it can probably be assumed that this patient was more than 1 year old. During a two and one-half year period, the murmur was reduced to only a faint systolic bruit. He concluded that the findings in this patient were probably due to a patent ductus arteriosus and that it was undergoing gradual occlusion under his observation.

Jacobi[6] reported a case which he had followed from infancy. He did not describe the murmur exactly but discussed the patient as a case of patent ductus

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Received for publication June 25, 1952.
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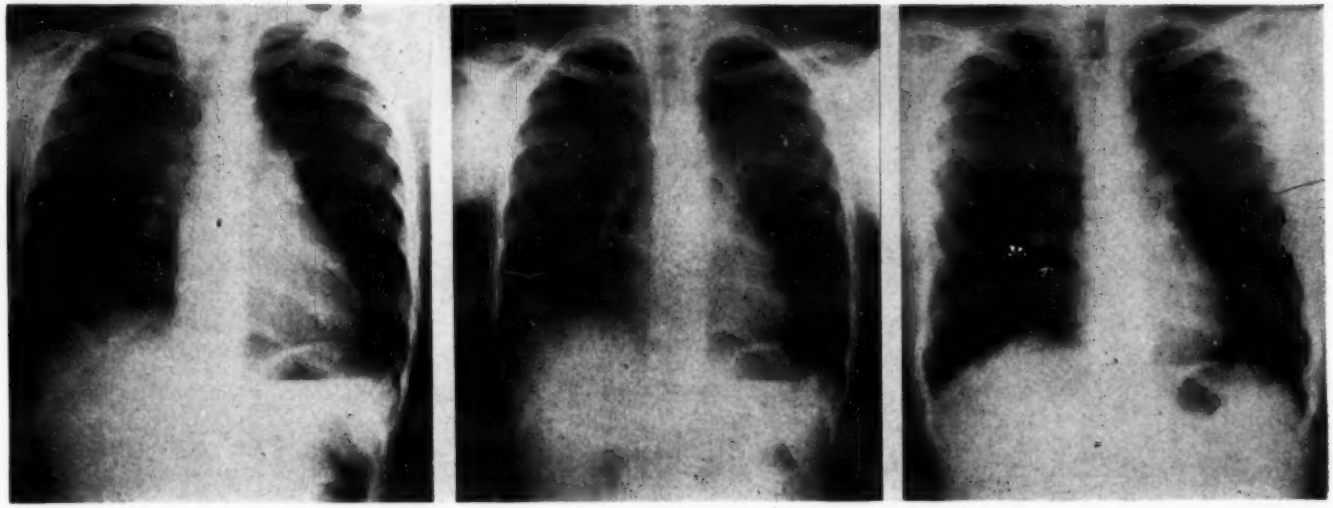

A. *B.* *C.*

Fig. 1.—*A*, Admission survey chest film of Nov. 9, 1942, in which the undivided portion of the pulmonary artery is prominent. *B*, Survey chest film of Sept. 16, 1944. The undivided portion of the pulmonary artery is less prominent than in *A*. *C*, Survey chest film of Oct. 4, 1951, which is within normal limits.

arteriosus. The murmur disappeared completely at the age of 9 or 10 years. Jacobi assumed that the ductus had closed.

Keys and Shapiro[7] made reference to two cases in which the signs of patent ductus arteriosus disappeared later in life. It was their opinion that this phenomenon was rare and that there was probably no need to consider it in evaluating the ultimate prognosis of the patient with patent ductus arteriosus.

Gilchrist[8] reported one case in which the murmur and x-ray changes of patent ductus arteriosus disappeared between the ages of 5 and 6.5 years. It was his opinion that late closure of the ductus arteriosus must be rare but that spontaneous closure up to the age of 10 years should be considered as a possibility.

In a discussion of the prognosis of patent ductus arteriosus, Benn[9] reported two cases in which the typical machinery murmur disappeared. However, due to persistence of an enlarged pulmonary artery (increased pulmonary artery index), pulmonary congestion, and enlarged heart in his first case, he concluded that the ductus had not closed. He thought that the ductus had not closed in his second case because of lack of change in the blood pressure during the period of observation. The blood pressure was 120/60 mm. Hg.

The continuous murmur of a patent ductus arteriosus may disappear in the presence of congestive heart failure, and there are reports of patients in whom the murmur has disappeared or has become atypical in the presence of subacute bacterial endarteritis.[10] In the case reported by Foulis[11] the murmur was absent twenty-five days before death, but, from his description, the patient was also in congestive heart failure at the time. Autopsy of this patient showed almost complete closure of the ductus arteriosus by a conical thrombus. Gibb[12] reported a case in which there was no history of heart disease or murmurs. No murmurs were heard on physical examination but *Staphylococcus albus* was cultured from the blood. Autopsy of this case showed the ductus arteriosus to be occluded by vegetations.

Jager[13] reported the case of a 55-year-old woman in whom thrombosis occurred on the roughened and calcified walls of the ductus arteriosus. No murmurs were noted clinically in this case. Autopsy showed no evidence of bacterial endarteritis.

With the foregoing considerations in mind, a case is presented in which the clinical, roentgenographic, and electrocardiographic findings were characteristic of patent ductus arteriosus, and in which the abnormalities have almost completely disappeared and no diagnosis of heart disease is possible at the present time.

CASE REPORT

The patient, a 14-year-old boy, has been seen in the Heart Station, University Hospital, as an outpatient on three occasions. The first time was in 1942 when he was referred to us by his local physician for evaluation of a heart murmur that had been discovered in 1939, when the patient was 2 years old. The patient was not cyanotic at birth and his growth and nutrition were

normal. He was normally active as an infant and child and no unusual dyspnea on exertion had been noted. The parents thought that when he was scolded or when there was marked exertion in the cold his lips became blue. There had been no illness suggesting rheumatic fever.

Examination showed a well-developed, healthy appearing boy of 5 years. There was no cyanosis or clubbing of the fingers. The tonsils were large. The left border of cardiac dullness was slightly lateral to the left midclavicular line and it was thought that slight enlargement might be present. The rate and rhythm were normal. The heart sounds were not unusual, and no abnormal findings were present at the apex. At the pulmonic area, a loud continuous murmur with rough accentuation in systole was heard. The blood pressure was 90/30 mm. Hg but the sounds could be heard below the cuff down to zero. The lungs were clear and physical examination was otherwise negative. The routine survey chest film reproduced in Fig. 1,*A* showed prominence of the undivided portion of the pulmonary artery and was reported to suggest congenital heart disease. Electrocardiograms, (Fig. 2,*A*) showed very large QRS complexes in the limb leads suggesting cardiac enlargement. On the basis of the above findings, a diagnosis of patent ductus arteriosus, probably uncomplicated, was made and the possibility that the ductus should be obliterated by surgical treatment was mentioned to the parents.

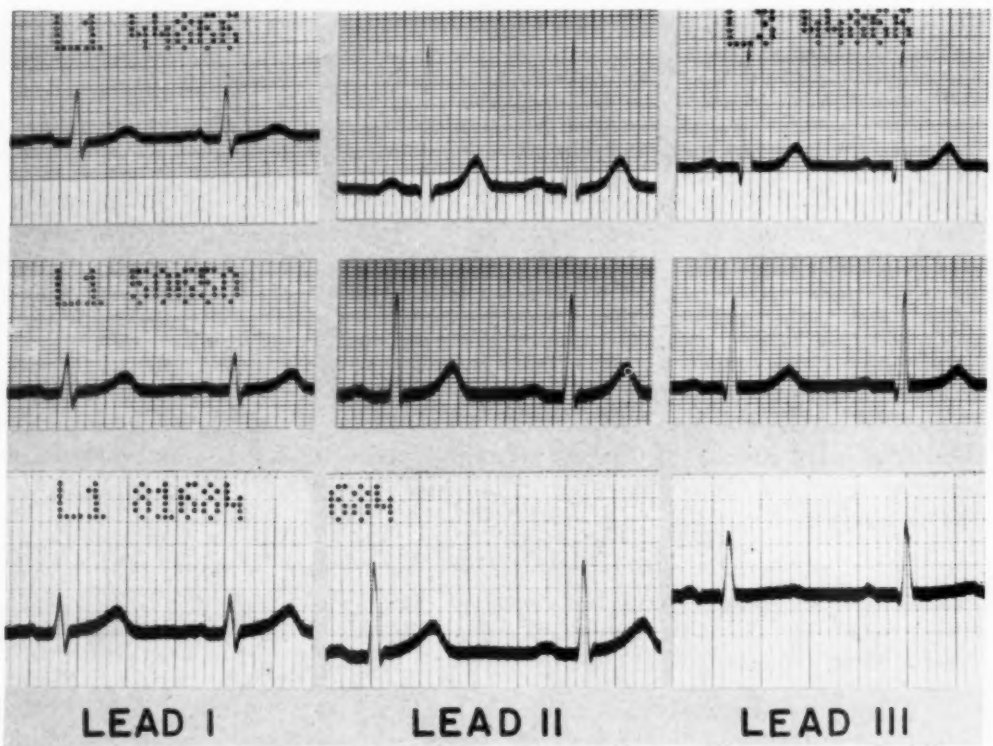

Fig. 2.—*A*, Electrocardiogram of Nov. 9, 1942, in which the QRS complexes are abnormally large. *B*, Electrocardiogram of Sept. 16, 1944, in which the QRS deflections, especially in Lead II, are smaller than in *A*. *C*, Electrocardiogram of Oct. 4, 1951, which is within normal limits.

The patient was seen on the second occasion in 1944 when he was 7 years old. For three weeks prior to this visit he had been listless and irritable, for no obvious cause, and had had a nonproductive cough. The parents did not think he had been having fever but they had not taken his temperature. No sore fingers or eruption on the skin had been noticed. Examination at this time revealed no significant change in the murmur or other cardiac findings. The blood pressure was 110/60 mm. Hg. The lungs were clear, the liver and spleen were not pal-

pable, and there was no edema. There was no cyanosis or clubbing of the fingers and no petechiae were seen. The survey chest film taken at this time (Fig. 1,*B*) was reported as negative. Regular chest films were also obtained at this visit and showed slight prominence of the pulmonary conus and pulmonary vascular pattern but no evidence of pulmonary disease. Electrocardiograms, (Fig. 2,*B*) were similar to those previously taken except for a definite decrease in the voltage of the QRS complexes, especially in Lead II. A patent ductus arteriosus was believed to be present, as before, and the possibility of subacute bacterial endarteritis was raised. The boy had a temperature of 99.0°F. while in the Heart Station and the parents were advised of the possible infection and told to take his temperature twice daily for at least one week.

The patient was seen for the third time on Oct. 4, 1951. He was 14 years old and returned to University Hospital because of an episode of pleuritic pain in the left anterior chest lasting for three days, occurring about three weeks before his visit to Ann Arbor. During the period of seven years since he was seen in 1944, the boy had grown and developed normally and there had been no serious illness or difficulty of any kind. Examination revealed a well-developed, healthy appearing boy with no complaints. His tonsils were large but examination of the heart and the rest of the body was well within normal limits. The loud continuous murmur heard on two previous occasions had disappeared and the only murmur audible was a fairly loud systolic murmur at the pulmonic area, present only after exercise. The blood pressure was 125/75 mm. Hg. The survey chest film (Fig. 1,*C*) was reported as normal and the electrocardiogram (Fig. 2,*C*) was also quite normal.

The findings at this third visit did not justify a diagnosis of heart disease of any kind since the systolic murmur at the pulmonic area would be classified without hesitation by any competent cardiologist as a functional murmur and of no significance.

DISCUSSION

The situation here is a very unusual one and were it not for the fact that the patient was seen by an experienced cardiologist (Dr. Franklin D. Johnston) at the time of all three of the visits to the hospital, one might have justifiable doubts regarding the existence of a patent ductus arteriosus in 1942 and 1944 and its subsequent disappearance. The changes in the roentgenograms (Fig. 1) and those in the electrocardiograms (Fig. 2) are sufficient to provide additional evidence favoring closure of an open ductus.

There is no way to explain with certainty the closure of the ductus arteriosus in the patient described above. Delayed spontaneous obliteration without infection cannot be excluded, but the author feels that low-grade infection with endarteritis and thrombosis leading to fibrosis and disappearance of the lumen within the ductus is a more plausible explanation. This process may have been going on at the time of his second visit to the hospital, but, if so, the infection never became important enough to cause symptoms that would point clearly to a lesion of this type. Surgical obliteration of the ductus in patients with subacute bacterial endarteritis is known to terminate the infection occasionally and thrombosis of the ductus, early in the course of the infection, may have occurred in this patient.

He will return for re-examination every six months during the next few years so that the permanence of the presumed closure may be checked.

SUMMARY

1. A patient is presented in whom a patent ductus arteriosus closed spontaneously between the ages of 7 and 14 years.

2. Although delayed closure of the ductus without infection cannot be excluded, subacute bacterial endarteritis, with thrombosis early in the disease, and subsequent spontaneous resolution of the infection and fibrosis of the ductus is considered a more likely cause in this patient.

I wish to thank Dr. Franklin D. Johnston for his assistance and criticism in the preparation of this report. The reported case was referred to University Hospital by Dr. Robert J. Cooper of Pontiac, Mich.

REFERENCES

1. Patten, B. M.: The Changes in Circulation Following Birth, Am. Heart J. **6**:192, 1930.
2. Christie, A.: Normal Closing Time of the Foramen Ovale and the Ductus Arteriosus, Am. J. Dis. Child. **40**:323, 1930.
3. Gross, R. E.: Surgical Management of the Patent Ductus Arteriosus, Ann. Surg. **110**:321, 1939.
4. Reid, M. R.: Discussion of Gross,[3] Ann. Surg. **110**:351, 1939.
5. Williams, E. C.: A Case of Patent Ductus Arteriosus, Rep. Soc. Study Dis. Child. **4**:310, 1904.
6. Jacobi, A.: Discussion of a Case Report by Hamilton, W. F., and Abbott, M. E., Tr. A. Am. Physicians **29**:308, 1914.
7. Keyes, A., and Shapiro, M. J.: Patency of Ductus Arteriosus in Adults, Am. Heart J. **25**:158, 1943.
8. Gilchrist, A. R.: Patent Ductus Arteriosus and Its Surgical Treatment, Brit. Heart J. **7**:1, 1945.
9. Benn, J.: The Prognosis of Patent Ductus Arteriosus, Brit. Heart J. **9**:283, 1947.
10. Hertzman, V. O., and Strong, G. F.: Patent Ductus Arteriosus, Canad. M. A. J. **61**:495, 1949.
11. Foulis, J.: On a Case of Patent Ductus Arteriosus, With Aneurism of the Pulmonary Artery, Edinburgh M. J. **29**:1117, **30**:17, 1884.
12. Gibb, W. T., Jr.: Acute Bacterial Endarteritis of a Patent Ductus Arteriosus, New York State J. Med. **41**:1861, 1941.
13. Jager, B. V.: Noninfectious Thrombosis of a Patent Ductus Arteriosus, Am. Heart J. **20**:236, 1940.

ANNOUNCEMENTS

AMERICAN ACADEMY OF FORENSIC SCIENCES

The American Academy of Forensic Sciences announces its fifth annual meeting which will be held Feb. 26-28, 1953, at the Drake Hotel, Chicago, Ill. All persons planning to present papers should submit their titles to Dr. Milton Helpern, Program Chairman, 106 E. 85th Street, New York 28, N. Y., before Dec. 1, 1952.

SOCIETY FOR THE ADVANCEMENT OF CRIMINOLOGY

The Society for the Advancement of Criminology will hold a one-day interim meeting Feb. 24, 1953, at Northwestern University Law School, Chicago, Ill. This meeting will immediately precede the 1953 meeting of the American Academy of Forensic Sciences, Feb. 26-28, at the Drake Hotel, Chicago. The SAC meeting will be of interest to all those engaged in police administration education programs on the college level, who have not been able to attend the annual meetings in California. The complete program will be announced shortly. All those interested in presenting papers should contact the Program Chairman, Professor Ralph F. Turner, Department of Police Administration, Michigan State College, East Lansing, Mich.